

Drug Delivery[®] Technology[®]

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TPM Platform: Does It Deliver?

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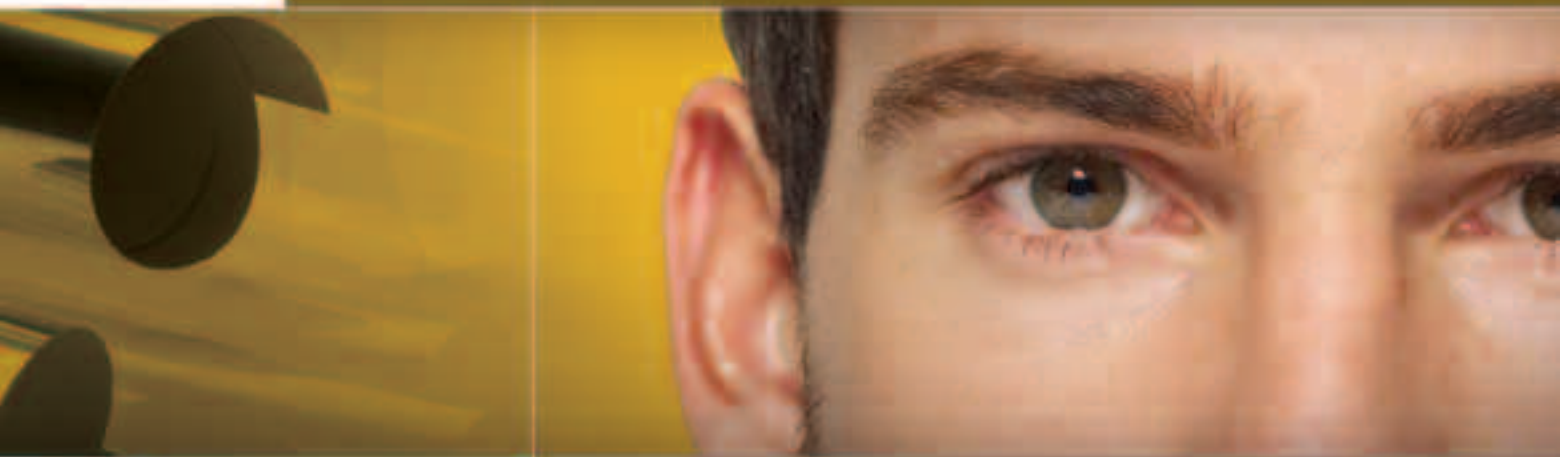
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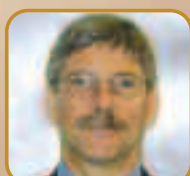
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ProStrakan Receives US FDA Approval for World's First Licensed Transdermal 5HT3 Receptor Antagonist

ProStrakan Group plc, the international specialty pharmaceutical company, recently announced it has received approval from the US Food and Drug Administration (FDA) for Sancuso, ProStrakan's novel, patent-protected transdermal patch for the prevention of chemotherapy-induced nausea and vomiting (CINV). ProStrakan expects to launch Sancuso in the US before the end of 2008, which is its first product launch in the US.

Sancuso, the world's first licensed transdermal 5HT3 receptor antagonist product, will be launched into a market worth \$1.3 billion in the US alone. As a patch, Sancuso offers cancer sufferers who are at risk of severe nausea and vomiting a new, patient-friendly treatment choice that is both non-invasive and non-oral. It was developed in-house by ProStrakan, from inception to launch, in 5 years and will be marketed by an exclusive US sales force, currently being established by ProStrakan in collaboration with NovaQuest (the partnering group of Quintiles).

"FDA approval of Sancuso means that ProStrakan remains on track to launch its first product in the US, the world's largest pharmaceutical market, later this year," said Dr. Wilson Totten, ProStrakan's Chief Executive Officer. This is a very significant breakthrough, both for patients and ProStrakan. The launch will make Sancuso available for the first time to prevent nausea and vomiting in chemotherapy patients. Significant challenges persist in the prevention of CINV, which jeopardizes the health of many chemotherapy patients and can deter them from continuing their cancer treatment. With peak sales potential in the order of 100 million dollars each, Sancuso's US approval and that of Abstral in Europe are pivotal events in allowing ProStrakan to become profitable in the next 2 years."

"We plan to file two further New Drug Applications with the FDA in the US for Fortigel and Cellegesic in the coming months. The NDA for Rapinyl, for which we acquired the US rights in July, will follow in 2009," he added.

ProStrakan has already established its US head office in Bedminster, NJ, and has recruited an experienced management team. Its US National Sales Manager is in place, together with seven Medical Science Liaison team members, who have now been trained and will liaise with oncologists and oncology nurses across the US. The company will continue to work in collaboration with its US strategic partner, NovaQuest (the managed partnership group of Quintiles

Transnational Corp.), to deploy its 67-strong national sales force.

Sancuso is a transdermal patch that delivers granisetron, an established 5HT3 receptor antagonist, steadily into the bloodstream for up to 7 days. Sancuso has been shown to be as efficacious as oral granisetron in preventing the side effects of nausea and vomiting in patients undergoing chemotherapy. Sancuso has the advantage of offering this protection through a single transdermal patch application, eradicating the need for repeated daily injections, thus reducing potential infection risk, or having to swallow multiple pills on a repeated daily basis, which is often not possible in cancer patients due to oral mucositis.

The FDA-approved Sancuso, for the prevention of CINV, based on the results of a multicentre Phase III randomized, double-blind, double-dummy controlled study comparing the efficacy, tolerability, and safety of Sancuso with once-daily oral granisetron (2 mg). The trial enrolled 641 patients who received moderately or highly emetic multi-day chemotherapy, and met its primary endpoint of non-inferiority of Complete Control of CINV compared to oral granisetron. Complete Control was defined as no vomiting and/or retching, no more than mild nausea, and no rescue medication from first administration of Sancuso until 24 hours after the last day of chemotherapy. The most frequent adverse event was constipation.

As part of the approval, the company has agreed to conduct certain post-approval clinical studies, including evaluations in children and the elderly. Launch stocks of Sancuso are being manufactured by Aveva Drug Delivery Systems, Inc., who specializes in the development and manufacture of transdermal drug delivery systems, and will supply commercial stocks of Sancuso for ProStrakan on an ongoing basis.

ProStrakan Group plc is a rapidly growing specialty pharmaceutical company engaged in the development and commercialization of prescription medicines for the treatment of unmet therapeutic needs in major markets. ProStrakan's head office is situated in Galashiels in Scotland. The company's development capabilities are centred on Galashiels and Bedminster, NJ. Sales and marketing of ProStrakan's portfolio of products are handled by commercial subsidiaries in the UK, US, France, Germany, Spain, and other EU countries.

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Abraxis BioScience & ProMetic BioSciences Enter License Agreements up to \$295 Million for Four Biopharmaceuticals

Abraxis BioScience, Inc. and ProMetic Life Sciences Inc. recently announced they have signed definitive agreements for the development and commercialization, on a world-wide basis (excluding China and Taiwan), of four biopharmaceutical products targeting underserved medical conditions. These represent market opportunities potentially exceeding \$600 million in annual revenue for Abraxis. The transaction includes an initial strategic investment by Abraxis in ProMetic of \$7 million at \$0.47 CDN per share as well as providing Abraxis rights to make optional investments of up to \$25 million. The transaction involves access to ProMetic's proprietary protein technologies to commercialize the biopharmaceuticals. Abraxis will fund all development costs to regulatory approval. The licensed products will be manufactured by ProMetic and commercialized by Abraxis.

"The strategic fit between our two companies has resulted in an agreement that makes key resources available to ProMetic while providing Abraxis with access to leading protein technologies and products with excellent market potential," said Patrick Soon-Shiong, MD, Chairman and CEO of Abraxis. "ProMetic is providing us with proven technologies enabling the development and manufacturing of four valuable therapeutics, while Abraxis' corporate and financial resources will significantly accelerate their commercialization."

The licensing agreements include up to \$8 million to ProMetic in potential development milestone payments; potential sales milestones in excess of \$287 million in addition to royalties on the net sales of the four products by Abraxis. Under a separate service agreement, ProMetic will perform product development activities on behalf of Abraxis, which translates into revenue for ProMetic starting in 2008. The combination of development milestones and service fees could represent revenue totaling \$34 million over the next 3 years for ProMetic. The first product is expected to reach commercial stage by 2011.

Additional revenue to ProMetic will result from the manufacturing of products for clinical trial requirements. Beyond that, the revenue opportunity to ProMetic is expected to significantly increase once the products have reached commercial status. Pursuant to the manufacturing agreement, ProMetic will supply Abraxis with bulk active ingredients. Abraxis will then perform the final formulation steps to dosage form for the four biopharmaceutical products.

"This transaction signifies the beginning of a new chapter for ProMetic. The equity component and the service agreement, in combination with ProMetic's other developing revenue streams, will fund the day-to-day operations of the company. Financing activities will only be undertaken if significant opportunities emerge to further expand ProMetic's business," said Mr. Pierre Laurin, President and CEO of ProMetic.

"The cash-flow contribution from these agreements is expected to be in the range of \$10 million in 2008 and each of the following 2 to 3 years prior to the first expected regulatory approval of the products," added Mr. Bruce Pritchard, ProMetic's CFO. "Once the licensed products reach commercial status, the nature of our revenue converts into manufacturing revenues, royalties, and sales milestones, all of which grow proportionately with Abraxis' sales performance."

Abraxis BioScience, Inc. is a fully integrated global biotechnology company dedicated to the discovery, development, and delivery of next-generation therapeutics and core technologies that offer patients safer and more effective treatments for cancer and other critical illnesses. The company's portfolio includes the world's first and only protein-bound chemotherapeutic compound (ABRAXANE), which is based on the company's proprietary tumor-targeting technology known as the nab platform. The first FDA-approved product to use this nab platform, ABRAXANE, was launched in 2005 for the treatment of metastatic breast cancer.

ProMetic Life Sciences Inc. is a biopharmaceutical company specialized in the research, development, manufacture, and marketing of a variety of commercial applications derived from its proprietary Mimetic Ligand technology. This technology is used in large-scale purification of biologics and the elimination of pathogens. ProMetic is also active in therapeutic drug development with the mission to bring to market effective, innovative, lower cost, less-toxic products for the treatment of hematology and cancer. Its drug discovery platform is focused on replacing complex, expensive proteins with synthetic drug-like protein mimetics.

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Antares Enters Agreement With Dr. Reddy's for Enhanced Dermatology Product Utilizing the ATD Gel Platform

Antares Pharma, Inc., a specialty pharmaceutical company focused on improving pharmaceuticals through advanced drug delivery systems, recently announced it has entered into a development agreement with Dr. Reddy's Laboratories, Inc. for the development of an innovative, topically applied product using Antares' ATD Gel platform, targeting specific receptor sites within the skin.

As part of the overall understanding between the parties, Antares will be responsible for development and commercial manufacturing of the product, and Dr. Reddy's will be responsible for clinical development and marketing. Dr. Reddy's will market the product through Promius Pharma, its US-based specialty dermatology business, upon final approval. Under the terms of this agreement, Antares will receive fees for all its development activities. Upon successful completion of this development, a license and supply agreement will be executed by the parties. The license and supply agreement would include mutually agreed upon up-front and milestone payments, product sales, and royalties.

"We look forward to developing another novel product utilizing our FDA-approved ATD gel with our partner Dr. Reddy's. In addition, this project signifies the initiation of utilizing our ATD system to deliver active ingredients topically, and not systemically, demonstrating the flexibility of our platform in the therapeutic field of dermatology," said, Jack E. Stover, Chief Executive Officer of Antares.

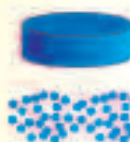
Antares' ATD gel technology is a patent-protected drug delivery system designed for the enhanced skin permeation of therapeutic entities. The technology is already validated in that it is the basis of an FDA-approved product (transdermal estradiol gel for the treatment of menopausal symptoms) and two Phase III clinical-stage products

(transdermal oxybutynin gel for overactive bladder and transdermal testosterone for female sexual dysfunction). Based on hydroalcoholic solvent systems containing a combination of permeation enhancers, ATD gel formulations are not only easy to use, but also ensure drugs are absorbed rapidly through the skin after once-daily application on the upper arms, shoulders, abdomen, or thighs. Clinical trials using different therapeutic actives have demonstrated efficacy and excellent skin tolerability.

Antares Pharma is a specialized pharma product development company committed to improving pharmaceuticals through its patented drug delivery systems. Antares has three validated systems: the ATD Advanced Transdermal Gel Delivery system; subcutaneous injection technology platforms (including Vibex disposable pressure-assisted auto injectors, Valeo/Vision reusable needle-free injectors, and disposable multi-use pen injectors); and Easy Tec oral disintegrating tablets (ODT). Two of the systems have generated FDA-approved products. The company's products are engineered to improve safety and efficacy profiles by minimizing dosing and reducing side effects while enabling improved patient compliance. The company's lead product candidate, Anturol, an oxybutynin ATD gel for the treatment of OAB (overactive bladder), is currently under evaluation in a pivotal Phase III trial. The Anturol trial is being conducted under an agreement reached with the US FDA under its special protocol assessment, or SPA process. Antares Pharma has corporate headquarters in Ewing, New Jersey, with subsidiaries performing research, development, manufacturing, and product commercialization activities in Minneapolis, Minnesota, and Basel, Switzerland.

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FLASH BEADS



Orally Disintegrating Tablets (ODT)

Cough Suppressants

- Dextromethorphan HBr ODT 15mg - Cherry Flavor
- Dextromethorphan HBr ODT 30mg - Cherry Flavor

Cough & Cold

- Zinc Vapor Action Sng - Cool Mint Flavor
- Acetaminophen 600mg ODT - Grape Flavor
- Acetaminophen 1600mg ODT - Grape Flavor
- Acetaminophen 325mg ODT - Grape Flavor



Decongestants

- Pseudoephedrine HCl 120mg - Orange Flavor

Anesthetics

- Benzocaine Sng - Menthol ODT 10mg - Cool Mint Flavor

Nausea and Vomiting

- Dimenhydrinate HBr ODT - 50mg - Orange Flavor
- Dimenhydrinate HBr ODT - 50mg - Orange Flavor

Stimulant and Stay Awake

- Caffeine 40mg - Taurine ODT 10mg - Cherry/Coffee Flavor

Joint Health

- Glucosamine 500mg ODT - Cool Mint Flavor

Dietary Supplements ODT

- Methylcobalamin 1mg ODT - Cherry Flavor
- Folic Acid 400mcg ODT - Orange Flavor

Flash Beads™ (Non-Melting Beads)

Cough Suppressants

- Dextromethorphan HBr Flash Beads 15mg - Cherry Flavor
- Dextromethorphan HBr Flash Beads 30mg - Cherry Flavor

Decongestants

- Pseudoephedrine Flash Beads 120mg - Orange Flavor

Anesthetics

- Benzocaine Sng - Menthol 10mg Flash Beads - Cool Mint Flavor

Expectorants

- Guaifenesin Flash Beads 180mg - Orange Flavor

Joint Health

- Glucosamine 500mg Flash Mint Beads - Lemon Lime Flavor

Bone Building

- Calcium 1000mg - Mag 100mg - Orange Flavor



Chewable Tablets

Anesthetics

- Benzocaine Sng - Menthol 10mg Chew Tabs - Cool Mint Flavor

Joint Health

- Glucosamine 500mg - Chaii 800mg - Lemon Lime Flavor

Bone Building

- Calcium 1000mg - Mag 100mg - Orange Flavor

Cough & Cold

- Zinc Sng Vapor Action Chew Tabs - Cool Mint Flavor



Chewables

Anesthetics

- Benzocaine Sng - Menthol 10mg Chew - Cool Mint Flavor

Cough & Cold

- Zinc Vapor Action Sng Chew - Cool Mint Flavor

Antacid

- Antacid 1177mg - Wild Cherry Flavor

Joint Health

- Glucosamine 500mg - Chaii 800mg - Lemon Lime Flavor



Bone Building

- Calcium 1000mg - Mag 100mg - Orange Flavor

GI Health

- Fiber 1.5gm - Glucosamine/Tropical Fruit Flavor
- Fiber 1gm - Calcium 1000mg - Chocolate Flavor
- Fiber 1.5gm - Vitamin C 60mg - Tropical Fruit Flavor

Weight Reduction

- Weight Reduction Fiber 1.5gm - Garcinia 250mg - Christmas Sng - Tropical Fruit Flavor



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Aegis Therapeutics Receives Patent for Growth Hormone Formulations for Metered Nasal Spray Delivery

Aegis Therapeutics LLC recently announced it has been awarded US Patent No. 7,425,542, titled Stabilizing alkylglycoside compositions and methods thereof. The patent provides broad protection for stabilized human growth hormone (hGH) formulations. Human growth hormone is a recombinant protein drug used in the treatment of pediatric and adult patients who have inadequate secretion of normal endogenous growth hormone. hGH is one of the first biopharmaceuticals to be developed and has achieved worldwide sales in excess of \$2 billion annually.

Like other protein therapeutics, including insulin, erythropoietin, and interferon, among others, hGH is sensitive to heat and agitation and subject to aggregation, a phenomenon that reduces the potency of protein drugs and increases unwanted and sometimes dangerous immunogenicity. As a result, protein therapeutics must be stored and shipped from the manufacturer to the pharmacy and ultimately to the patient under an uninterrupted chain of refrigerated conditions referred to as the cold chain. Failure to maintain the cold chain during shipment can compromise the effectiveness of protein drugs.

The Aegis ProTek technology has been employed to create stabilized formulations of hGH, insulin, antibodies, and other protein drugs that remain unchanged even after continuous agitation for many weeks or months at elevated temperatures. The patented formulations are suitable for intranasal delivery via a simple metered nasal spray as well as by standard injection or external drug infusion pump.

Human growth hormone products are sold by a number of the world's leading pharmaceutical companies, including Genentech, Sandoz, Sanofi, Novo Nordisk and Eli Lilly. Generic or so-called bioequivalent versions of human growth hormone are in development as the original growth hormone patent approaches expiration. Aegis ProTek technology is expected to provide patients with safer, more convenient, non-injectable delivery options while extending the effective patent life of hGH and other protein drugs.

Aegis Therapeutics LLC is a drug delivery technology company commercializing its patented or proprietary drug delivery and drug formulation technologies through product-specific licenses. Its Intravail drug delivery technology enables the non-invasive delivery of a broad range of protein, peptide, and non-peptide macromolecular therapeutics that can currently only be administered by injection. Aegis' Intravail absorption enhancement agents provide exceptionally high and unmatched bioavailability performance, comparable in efficiency to subcutaneous injection, via the intranasal administration route. Intravail has also been successfully applied to buccal, oral, and rectal administration of both small molecule and peptidic drugs. The ProTek technology allows creation of proprietary, easily manufacturable, and stable aqueous or lyophilized dosage forms that maintain the integrity and physiological activity of many protein and peptide therapeutics. ProTek technology is applicable to injectable, intranasal, and other dosage forms of peptide or protein therapeutics.

Biovail Acquires Prestwick Pharmaceuticals

Biovail Corporation recently announced it has acquired Prestwick Pharmaceuticals, Inc., a privately held, US-based pharmaceutical company that holds the Canadian and US licensing rights to Xenazine (tetrabenazine tablets). Xenazine was recently approved by the US FDA for the treatment of chorea associated with Huntington's disease. Xenazine was granted Orphan Drug designation by the FDA, which provides the product with 7 years of market exclusivity in the US.

Prestwick recently entered into an exclusive agreement with Ovation Pharmaceuticals, Inc., a leading US-based specialty biopharmaceutical company, to commercialize Xenazine in the US. The product's commercial launch is anticipated late 2008.

"We are delighted to have acquired Prestwick, and with it, an interest in Xenazine, the first and only FDA-approved treatment for any symptom of Huntington's disease," said Biovail Chief Executive Officer Bill Wells. "The transaction meets all of our acquisition criteria, and represents Biovail's first commercial exposure to specialty markets in central nervous system, or CNS disorders. The acquisition is another important step in the implementation of our New Strategic Focus."

Under the terms of the agreement, Biovail has paid \$100 million to acquire 100% of Prestwick Pharmaceuticals, Inc. and related license rights. Beyond Xenazine, the acquisition also provides Biovail with other early stage products, including Lisuride Sub Q (advanced Parkinson's disease), Lisuride Patch (Parkinson's disease), and D-Serine (Schizophrenia).

Biovail will commercialize tetrabenazine tablets in Canada (marketed under the Nitoman brand name) through the Biovail Pharmaceuticals Canada sales force. Biovail will pay a variable supply price that ranges from 50% to 67% of net sales to Cambridge Laboratories (Ireland) Ltd., the worldwide license holder of tetrabenazine. In addition, Biovail holds an option to develop future related products with Ovation for the US market in conjunction with Cambridge.

The transaction is expected to be accretive to both earnings per share and cash flows in 2009.

Prestwick recently entered into an exclusive supply and marketing agreement with Ovation Pharmaceuticals, Inc. for Xenazine in the US. Following Biovail's acquisition of Prestwick, Biovail will supply the product to Ovation for a variable percentage of the product's annual net sales. For net sales up to \$125 million, Biovail's supply price will be 72% of net sales. Beyond \$125 million, Biovail's supply price will be 65% of net sales. At both tiers, Biovail will pay a supply price of 50% of net sales to Cambridge.

Ovation will market Xenazine to US specialists through a 48-person sales force, which already markets a number of other products targeting CNS disorders, including epilepsy and Attention Deficit Disorder. As part of the agreement, Biovail holds an option to co-promote Xenazine in the US. Should this option be exercised, Biovail has the right to utilize Ovation's existing infrastructure to assist in the recruitment, training, and operational management of a sales force.

Xenazine was approved by the FDA on August 15, 2008, for the treatment of chorea associated with Huntington's disease, based on the results of a double-blind, placebo-controlled, Phase III study that found Xenazine significantly reduced patients' chorea burden, improved global outcome scores, and was generally safe and well tolerated. Additional post-marketing preclinical studies further elucidating the safety profile of the product will be conducted. Xenazine has been available in Europe for more than 30 years and in Canada since 1996.

Biovail Corporation is a specialty pharmaceutical company engaged in the formulation, clinical testing, registration, manufacture, and commercialization of pharmaceutical products. The company is focused on the development and commercialization of medicines that address unmet medical needs in niche specialty CNS markets.

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Generex Announces Enrollment of More Than 200 Subjects in Oral-lyn Phase III Trial

Generex Biotechnology Corporation, a leader in drug delivery for metabolic diseases through the inner lining of the mouth, has reached the enrollment milestone of more than 200 subjects in the company's pivotal Phase III clinical trial of Generex Oral-lyn, its flagship proprietary prandial oral insulin spray product. There are 74 sites in the US, Canada, Bulgaria, Poland, Romania, Russia, and Ukraine actively screening and enrolling subjects.

"The Generex Oral-lyn trial is now well underway and we are satisfied that the team's efforts in setting up the project and selecting the sites for participation translated into such fast enrollment rates. We look forward to continue enrolling additional qualified subjects to reach our next project milestone on schedule in the coming weeks," said Diana Fowler of OSMOS Clinical Research, Inc. of San Francisco, California. OSMOS is the company's provider for the global project management

services for the trial.

The Phase III study will involve up to 750 subjects with type-1 diabetes mellitus at centers in the US, Canada, Bulgaria, Poland, Romania, Russia, and Ukraine. The objective of the long-term study is to compare the efficacy of Generex Oral-lyn and the company's RapidMist Diabetes Management System with prandial injections of regular human insulin as measured by HbA1c.

The company believes that Generex Oral-lyn will offer a safe, simple, fast, effective, and pain-free alternative to prandial insulin injections, which will improve subject compliance with therapeutic regimens, thereby delaying the progress of diabetes and the onset of its myriad complications. Generex Oral-lyn is presently approved for commercial sale in India and Ecuador.

Pharmatek Announces Opening of New Highly Potent & Cytotoxic Development & Manufacturing Facility

Pharmatek, a pharmaceutical chemistry development organization supporting the pharmaceutical industry, recently announced the opening of its highly-potent and cytotoxic facility located in San Diego, CA. The 18,000-sq-ft facility includes newly constructed analytical and formulation development laboratories and cGMP manufacturing suites dedicated to the development of highly potent and cytotoxic drug product for early phase clinical trials.

"Highly potent and cytotoxic compounds are among the most sensitive drugs to handle and produce," said Kevin Rosenthal, Director of Manufacturing for Pharmatek. "Our primary goal when designing the facility was to optimize product quality while ensuring operator safety to guarantee our clients' drug candidates move smoothly from discovery to clinical trials."

The facility holds a State of California Food and Drug Branch (FDB) Drug Manufacturers License and is currently working on a number of highly potent development projects. The FDB license

authorizes Pharmatek to manufacture and ship clinical material from its state-of-the-art highly potent and cytotoxic manufacturing and development site.

"The facility is a significant addition to our service offering," added Timothy Scott, President of Pharmatek. "We are always looking for ways to better meet our client's drug development outsourcing needs, and the highly potent and cytotoxic facility strengthens our ability to provide a broader level of services to our clients."

Pharmatek Laboratories Inc. is a premier pharmaceutical chemistry development company providing full-service pharmaceutical chemistry product development for the pharmaceutical industry. Pharmatek focuses on bringing client compounds from discovery to the clinic with services that include compound selection, analytical development, preformulation testing, formulation development, GMP manufacturing, stability storage and testing, and highly potent and cytotoxic drug development.

Cirrus Pharmaceuticals Expands Service Offerings by Adding cGMP-Compliant Walk-In Stability Chambers

Cirrus Pharmaceuticals, Inc. recently announced the expansion of its current capacity for stability storage via the addition of three LUWA Walk-In Stability Chambers. Cirrus will add three large-capacity chambers, each with 1,100 cubic feet of storage space. These chambers will be cGMP compliant, meeting FDA and ICH guideline requirements for stability.

"With an increase in our existing and new client sponsor requests for long-term stability storage and testing, expanding our capacity is a logical investment in Cirrus Pharmaceuticals' progression as a contract research service provider," said Jean-Marc Bovet, PhD, Executive Senior Vice President.

The new additions include the following storage conditions: 25°C/60% RH storage (Long-Term Conditions), 30°C/65% RH storage (Intermediate Conditions), 40°C/75% RH storage (Accelerated Conditions).

Cirrus Pharmaceuticals, Inc. is a contract product development

company assisting biotechnology and pharmaceutical companies with dosage form development projects. Cirrus works with start-up, mid-size, and multinational companies to provide a broad array of R&D services, including physical and chemical characterization, formulation development, stability testing, container/closure selection, process development, as well as scale-up and technical transfer to manufacturing.

With the expansion to cGMP-compliant Walk-In Stability Chambers, Cirrus will be able to increase its current core capabilities of formulation and strategic product development services for various dosage forms, including inhalation, nasal, parenteral, oral, topical, and transdermal. In addition, Cirrus will enhance its release testing and stability testing in support of clinical trials, IND, and NDA submissions. Validation of the chambers, including temperature and humidity mapping and monitoring systems, are on schedule for completion by November of this year.

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DSM & LibraGen Sign Agreement to Co-Develop Transaminases for Production of Chiral Amines

DSM and LibraGen, a bacterial diversity-based process and discovery specialist, recently announced they have signed an agreement to co-develop new omega-transaminases for production of chiral amines. Under the terms of the partnership, LibraGen will use its proprietary enzyme discovery and development to identify new enzymes for efficient conversion of a large spectrum of ketons into optically pure R- and S-amines, a compound class highly relevant for fine chemicals and pharmaceuticals industries.

DSM will produce the enzymes at industrial scale using DSM's fermentation capabilities and proprietary expression platform, PluGbug. LibraGen will sell the enzymes in kit form, and both parties will use them for screening activities and the development of biocatalytic processes for third parties.

"This collaboration with LibraGen grows the number of available large-scale biocatalysts and will contribute to increasing competitiveness of the transaminase technology for production of chiral amines" said Oliver May, Competence Manager Biocatalysis at DSM Pharmaceutical Products.

"In addition, by combining LibraGen's enzyme discovery and DSM's manufacturing capabilities, the development timelines from enzyme discovery and screening to final product delivery to our customers will be significantly reduced," added Ronald Gebhard, R&D Director at DSM Pharmaceutical Products.

"We are delighted that we have signed this partnership with DSM," said Renaud Nalin, CEO of LibraGen. "It marks another step forward in the development of LibraGen's industrial biocatalysis capabilities. Customers of DSM and LibraGen will be able to use these new enzymes on a laboratory or industrial production scale to produce intermediates and APIs, thus making our response to market demands even more effective."

LibraGen expects this alliance to bring the company additional openings to provide its services to the fine chemicals, pharmaceutical, and cosmetics customers, and to develop and optimize enzymatic synthesis processes for complex molecules.

LibraGen, Toulouse, France, specializes in the development of innovative bioprocesses for molecule synthesis using biocatalysis for fine chemicals, cosmetics, and pharmaceutical industries. One of LibraGen's key assets is its ability to look for high-performance enzymes in bacteria populations that have not previously been explored and convert them into production tools. By combining the skills needed to go from R&D to pilot production, LibraGen is fulfilling a market need by giving its customers high-performance and competitive synthesis solutions. Since the company was set up in 2001, LibraGen's reactivity and innovation has resulted in its becoming the exclusive producer of active enzymes for a number of third parties.

DSM Pharmaceutical Products is a global provider of high-quality custom contract manufacturing and development services to the pharmaceutical and biopharmaceutical industries. DSM contract manufacturing services include chemical development; registered intermediates; registered starting materials; APIs; fermentation; mammalian cell production of monoclonal antibodies and proteins; formulation development; clinical trial manufacturing; and finished dose form manufacturing of solids, semi-solids, and scheduled drugs, aseptic liquid, and lyophilized products.



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Spherics Announces Sale of Novel Proprietary Bioadhesive Polymers & Oral Drug Delivery System

Spherics, Inc. recently announced that all oral drug delivery intellectual property will be sold at a sealed bid auction on October 10, 2008 (at press time). Spherics' proprietary anhydride-based hydrophobic thermoplastic polymers, Spheromers, have superior conventional hydrophilic bioadhesive polymers. These polymers improve drug performance by increasing absorption and residence time in specific regions of the gastrointestinal (GI) track.

BIOGIT (BIOadhesive Gastro-Intestinal Targeted system) and BIOROD (BIOadhesive Rate-controlled Oral Delivery system) were developed at Spherics. These are advanced, bioadhesive polymer-based oral drug delivery systems that offer the flexibility of achieving a variety of drug-release profiles and offer advantages in a number of applications, which include significantly increasing the bioavailability of drugs that have a narrow absorption window, ability to deliver drug combinations of varying properties either simultaneously or sequentially in a controlled manner, improved and sustained delivery of drugs in the treatment of local GI disorders, ability to alleviate food effect for drugs known to have their PK profiles influenced by meals, and ability to release drug in a delayed pulse or two pulse release manner (chronotherapy).

Spherics has built a strong intellectual property position around its drug delivery technologies and products. The company has a broad range of issued US and international patents that they have applied to their four central nervous system products. These patents cover polyanhydride-based bioadhesive polymers and nanotechnology (PIN). In addition to these issued patents, Spherics has filed numerous applications covering compositions of matters of its proprietary polymers (SPHEROMERS), novel oral delivery systems (including BIOGIT), BIOROD, and PIN, manufacturing methods, methods of use, formulations, and product compositions.

Human Genome Sciences Strikes Biopharmaceutical Deal With Hospira

Human Genome Sciences, Inc. recently announced it entered a manufacturing alliance with Hospira Inc., agreeing to manufacture, develop, and sell supplies of some of Hospira's biopharmaceutical products. The companies did not disclose financial terms of the deal or identify the products HGS will make. HGS also said it entered into a marketing services agreement with Eden Biosciences Ltd. this past August. Under that deal, Eden will help HGS identify potential clients for its manufacturing and late-stage process development services.

"We see potential for \$30 to \$60 million in revenue from manufacturing alliances, including this alliance with Hospira, throughout the next 3 to 4 years," said Curran Simpson, HGS' Senior Vice President of Operations.

Analysts believe the deal will help the company cover the costs of developing its drug candidates, including Albuferon and Lymphostat-B, which are both in late-stage testing.

"The deal allows HGS to continue focus on advancing the company's drug pipeline while generating revenue from existing manufacturing capability," added Piper Jaffray Analyst Edward Tentoff. "Because of the time it takes for clinical development, these capabilities came online early, so as a result, they have unutilized capacity that they are using these types of deals to monetize."

The analyst said both drugs could be approved in 2010. Albuferon is a treatment for hepatitis C, and Lymphostat-B is an experimental treatment for lupus.

Capricorn Pharma & Teva Pharmaceuticals USA Enter Into Agreement

Capricorn Pharma Inc. recently announced it has entered into an agreement with Teva Pharmaceuticals USA to develop products using Capricorn's proprietary KORKOAT technology platform. KORKOAT beads accommodate high drug loads; modified drug release can be achieved by incorporating release-modifying agents inside the bead, in the coating, or in both.

"We are honored and pleased to enter into this agreement with Teva," said S. Rao Cherukuri, Founder, President, and Chief Executive Officer of Capricorn. "We are proud of our technologies, which offer flexible solutions to difficult formulation challenges. We believe this agreement further validates our commercialized oral drug delivery technology platforms and Capricorn's proprietary encapsulation processes."

Frederick, Maryland-based Capricorn Pharma is a specialty oral drug delivery systems company that develops, commercializes, and manufactures pharmaceutical products. The company has five commercialized oral drug delivery technology platforms and seven commercialized encapsulation processes.

Capricorn Pharma is organized into three business segments: Specialty Pharma, Specialty Consumer Health Care, and Microencapsulations. Seven patents have been issued to the company, and several applications are pending. The company's state-of-the-art, cGMP manufacturing facility is located in Frederick, where the company was founded in April 2000 by S. Rao Cherukuri.

Teva Pharmaceuticals USA is a leading generic pharmaceutical company, marketing products from a wide range of therapeutic areas. Based in North Wales, Pennsylvania, Teva Pharmaceuticals USA is a wholly owned subsidiary of Teva Pharmaceutical Industries Ltd., one of the largest generic pharmaceutical companies in the world and among the top 20 pharmaceutical companies of all types.

TestPak Launches New Pharma DDS Compliance Package

TestPak, the NJ-based healthcare contract packager, recently announced its launch of its newest child-resistant and senior-friendly compliance packaging system, Stora Enso's Pharma DDS. The addition of this design further strengthens TestPak's wide range of compliance packaging offerings.

"We are very pleased to introduce DDS to our line-up because it adds another outstanding compliance packaging option for our customers. We have high expectations for DDS because of its ease of use and cost effectiveness," said Bill Eveleth, Vice President of Sales and Marketing at TestPak.

Based on initial customer inquiries, the company already has a number of design applications on the drawing board.

"Stora Enso appreciates the dedication of TestPak toward the pharmaceutical compliance packaging market. The adoption of Pharma DDS further strengthens our cooperation with TestPak and provides a great avenue to the market," added Ralph Mendoza, Sales Manager for Stora Enso Pharmaceutical Solutions, during the signing



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Pharma DDS is a highly flexible and reclosable system with the capacity to contain a 30-count supply of most solid dose products, and it can be tailored to fit most any blister design. Its unique opening lock feature requires only limited manual dexterity and thus provides great ease of use. DDS has been tested successfully in the United States and in Europe for child-resistance and senior friendliness, fully meeting F=1 child-resistant performance.

"We were also attracted by the use of renewable paperboard materials and the fact that this system can be assembled on high-speed equipment, providing considerable cost savings," noted Mr. Eveleth.

Founded in 1983, TestPak offers contract packaging, product development, and logistics services to the pharmaceutical and nutritional industries. With modern FDA-registered sites in Whippany, NJ, the company provides the highest level of flexibility, quality, and responsiveness, from small packaging runs to high-volume production to turnkey product launches.

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Valeant Pharmaceuticals Signs Agreement to Acquire Coria Laboratories

Valeant Pharmaceuticals International recently announced it has signed a definitive agreement to acquire Coria Laboratories, Ltd., a privately held specialty pharmaceutical company focused on dermatology products in the United States. This transaction significantly expands Valeant's business in the US and enhances the company's dermatology franchise through the acquisition of key products, which complement its current portfolio. Current annualized net sales are approximately \$40 million.

Under the terms of the agreement, Valeant will purchase all of the outstanding shares of Coria from its parent company, DFB Pharmaceuticals, Inc., and other shareholders for \$95 million, subject to certain adjustments. The transaction is expected to close following the expiration or early termination of the waiting period under the Hart-Scott-Rodino Antitrust Improvement Act of 1976, as amended.

"Valeant is committed to growing our dermatology franchise, and this acquisition is a key step in transforming this business in the US and gaining the critical mass and profitability we need," said J. Michael Pearson, Chairman and Chief Executive Officer of Valeant. "The acquisition of Coria provides Valeant with access to a unique product portfolio,

which includes both prescription and OTC products, additional pipeline opportunities for the future, and a talented dermatology workforce. With the identified synergies between the two companies, we expect this transaction will be accretive to our earnings in 2009."

The Coria transaction will add several marketed dermatology products, including the CeraVe Skin Care Line, Cloderm Cream for the treatment of dermatoses, Akne-Mycin and Atralin for the treatment of acne, and Salex for the treatment of hyperkeratotic skin disorders, as well as Tetrax Cream for the treatment of hand dermatitis, which is expected to be launched later this year. In addition, Coria has several products under development, including line extensions for the CeraVe brand product line.

Valeant Pharmaceuticals International is a multinational specialty pharmaceutical company that develops, manufactures, and markets a broad range of pharmaceutical products primarily in the areas of neurology and dermatology.

Coria Laboratories, Ltd. is a privately held pharmaceutical company based in Fort Worth, TX, specializing in research, development, and marketing of branded prescription and OTC dermatology products.



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Sagent Pharmaceuticals Acquires Rights to Multi-Chamber Syringe Technology; Launches Device Division

Sagent Pharmaceuticals, Inc., a privately held specialty pharmaceutical company, recently announced the acquisition of Infusive Technologies' proprietary, patented, multi-chamber, sequential-dose syringe technology.

Sagent's innovative, dual-chamber syringe enables the sequential administration of two separate intravenous (IV) medications with a single syringe push, thereby replacing two syringes with one.

The benefits of this single delivery capability include increasing the speed and ease of drug administration; reducing risk of hospital acquired infection by reducing the number of connections; lowering the risk of drug administration or sequence errors, and quicker delivery of emergency medicines requiring an immediate sequential flush. The unique dual-chamber syringe can accommodate lyophilized, powder, or liquid formulations in the front chamber combined with diluents, saline, or heparin flush in the rear chamber.

"We believe that this dual-chamber syringe technology has far-reaching benefits, which will allow healthcare providers to deliver multiple drugs more quickly and more safely than with multiple syringes," said Jeffrey M. Yordon, Chairman, Founder, and Chief Executive Officer of Sagent Pharmaceuticals. "The simplicity and functionality of this device yield near-term opportunities for use with both proprietary and multi-source pharmaceutical products. We welcome Infusive's Chief Executive Officer, Bradley C. Robinson, to Sagent in his role as President of Sagent's newly created device division, Sagent Technologies. The creation of Sagent Technologies

marks an important milestone for the company, as it enhances our ability to provide a broad range of differentiated product offerings to healthcare providers."

"We look forward to introducing a prefilled format of the dual-chamber syringe to Sagent's US customers in 2009," added Mr. Robinson. "Syringes based on our unique, patented technologies have the potential to dramatically improve the delivery of IV medications, reduce the risk of medical error and hospital-acquired infection, while at the same time lowering costs for healthcare providers. Infusive was immediately impressed that Sagent not only is committed to providing quality IV medications, but also to providing IV medications in delivery systems designed to enhance effectiveness and improve patient safety. I look forward to joining Mr. Yordon and the team at Sagent and to quickly make this exciting new device available to patients and caregivers."

Sagent Pharmaceuticals, founded in 2006, is a privately held specialty pharmaceutical company focused on developing, manufacturing, sourcing, and marketing pharmaceutical products with a specific emphasis on injectable products. Sagent has created a unique, global network of resources, composed of rapid development capabilities, sophisticated manufacturing, and innovative drug delivery technologies, quickly yielding an extensive portfolio of pharmaceutical products that fulfills the evolving needs of patients. Sagent currently has more than 200 products in development.

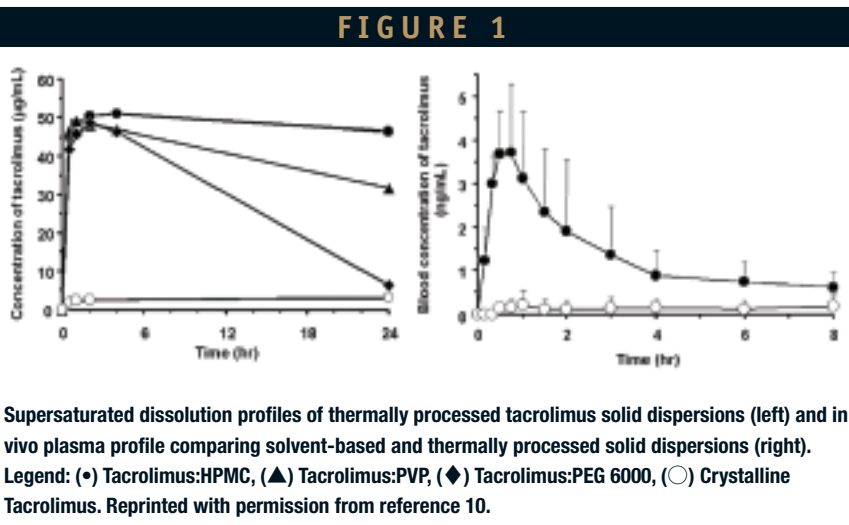
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Formulating Compositions to Achieve Enhanced Oral Bioavailability Through Supersaturation

By: James C. DiNunzio, MS; Dave A. Miller, PhD; James W. McGinity, PhD; and Robert O. Williams III, PhD

INTRODUCTION

The development of computational chemistry and high throughput screening has allowed for substantial progress in the way drug substances are developed. R&D efforts from remote areas of the world have evolved from tediously collecting and analyzing compounds in the bench-top laboratory to engineering and rapidly assessing those compounds for potential activity in the human body. High throughput screening has resulted in a multitude of new chemical entities (NCEs) capable of treating a variety of disease states; however, many of these compounds have also shown a substantial decrease in oral bioavailability over their predecessors, hindering the development of orally administered compositions. A variety of molecular properties have been identified in association with low bioavailability, including high molecular weight (> 500), log P values greater than 5, the number of hydrogen bond donors present on the molecule exceeding 5, and 10 or more hydrogen bond acceptor sites on the molecule.¹ Additionally, the number of rotatable bonds on a drug molecule, generally when greater than 10, has also been correlated with reduced oral bioavailability as a result of the entropic penalty associated with achieving conformations necessary to facilitate absorption.² Specifically for oral delivery, Biopharmaceutics Classification System (BCS) class II poorly water-soluble compounds have been shown to exhibit bioavailability relative to the dissolution rate of the drug product, with increased dissolution rates providing improved oral



bioavailability.^{3,4} It has been reported that 40% to 60% of NCEs in development have solubility issues, of which 15% to 30% can exhibit some improvement in dissolution rate through modification of the drug crystal structure.⁵⁻⁷

Throughout the past decade, there has been an explosion of new technologies and formulation strategies capable of addressing poor oral bioavailability due to low aqueous solubility, including: crystal engineering, co-crystal formation, nanoparticle production, cyclodextrin complexation, and amorphous formation. Each of these processes seeks to maximize the dissolution rate through modification of the intermolecular interactions and/or reduction of surface area that often results in supersaturation, or the ability of a formulation to provide drug concentrations in excess of the equilibrium solubility. Ultimately, however, these formulations eventually return the drug concentration to its equilibrium solubility due to the

thermodynamic instability associated with this state, which can result in incomplete and variable oral bioavailability. This review describes the underlying mechanisms for solubility enhancement from supersaturatable systems, as well as current applications of solid dispersion systems for bioavailability enhancement.

MECHANISMS FOR ACHIEVING SUPERSATURATION

The current development of formulations capable of achieving supersaturation has been focused primarily on the development of metastable polymorphic forms, nanomaterials, and solid dispersions, each of which are capable of achieving high solubilities due to inherent kinetic and thermodynamic properties of the system. Solid dispersions have recently gained significant popularity for the production of pharmaceuticals and can be defined as an intimate mixture of one or more active

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ingredients in an inert carrier or matrix at solid state prepared by thermal, solvent, or a combination thereof of processing techniques.⁸ By developing these compositions, it is possible to create formulations with the smallest possible drug domains (the individual molecules dispersed within a solid carrier, which are termed solid solutions). With solid dispersions, it is possible to maximize the solubility enhancement while increasing physical stability through proper selection of excipients when compared to polymorphic screening.

One of the most frequently cited properties of these systems is the dissolution rate of the system, which is increased due to the enhancement of surface area. As particles decrease in size, the total surface area per mass increases significantly. According to the Noyes Whitney equation, the dissolution rate will change in proportion with the surface area. Additionally, changes in metastable equilibrium solubility have also been reported due to decreases in particle size. According to the Ostwald-Freundlich equation (Equation 1), the solubility of a material is proportional to the exponential inverse of the particle diameter, where S is the saturation solubility of the material, S_∞ is the saturation solubility of an infinitely large particle, γ is the interfacial tension, M is the compound molecular weight, r is the particle radius, ρ is the density, R is a gas constant, and T is the temperature.⁹ By developing smaller particles, an enhancement in the overall magnitude of kinetic solubility can be achieved in addition to the rate at which that solubility is attained.

Equation 1.

$$S = S_\infty e^{\left(\frac{2\gamma M}{r\rho RT}\right)}$$

Crystal structure of the material is the other major property frequently cited in the literature for solubility enhancement.

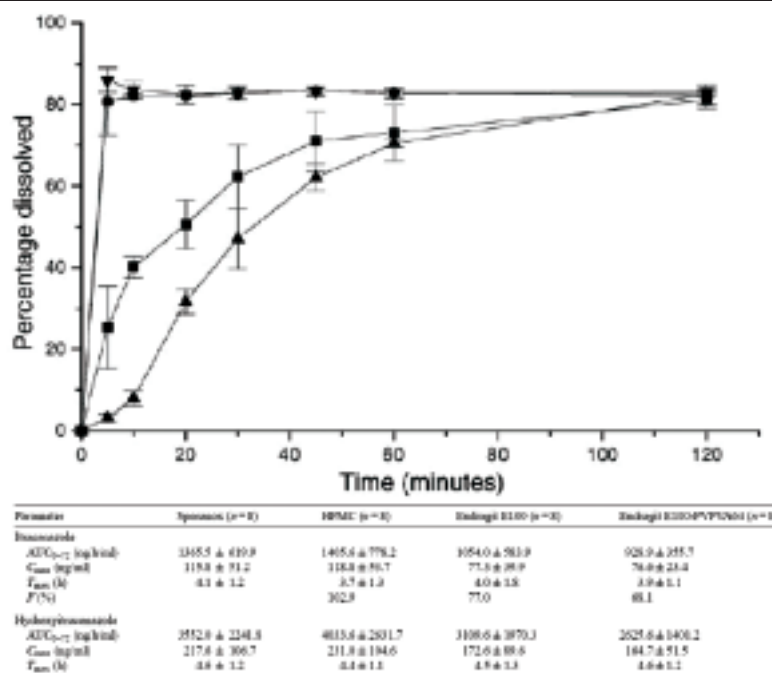
Pharmaceutical APIs may exist in a variety of crystal structures, commonly referred to as polymorphs, as well as amorphous forms, which lack any type of long- or short-range order associated with a crystalline material. When examining the dissolution process, it can actually be viewed as two separate and discrete steps: dissociation of the solute molecules from the crystal lattice and solvation of solute molecules. Modifications of the crystal structure can be used to reduce the intermolecular interactions and facilitate the dissolution of the drug substance. Ultimately, these forms offer transient solid-state properties and will eventually transition to the thermodynamically stable form of the drug substance. Detailed polymorphic screening and formulation optimization can be used however to provide compositions that are stable for pharmaceutically relevant timescales.

As previously mentioned, an extensive

portfolio of technologies has been developed to exploit these mechanisms of solubility enhancement. Particle size reduction processes, including “top-down” and “bottom-up” technologies, which maximize surface area to exploit the kinetic and thermodynamic advantages offered by size reduction. Molecular complexation techniques and solid solutions reduce the intermolecular interaction to facilitate dissociation while providing the theoretically smallest possible structure for dissolution (ie, the individual drug molecule). Additionally, formulation techniques, such as the incorporation of hydrophilic polymers and surfactants have been shown to further enhance the dissolution rate through improved wetting of microscopic drug domains within the composition.

Traditional dissolution testing is conducted under sink conditions, meaning that the amount of material added to the

FIGURE 2



Supersaturated dissolution profile of itraconazole solid dispersions (top) and pharmacokinetic data from human studies (bottom). Legend: Sporanox® (▲), HPMC extrudate (■), Eudragit® E100 extrudate (▼), and Eudragit® E100-PVPVA64 extrudate (●). Reprinted with permission from reference 11.

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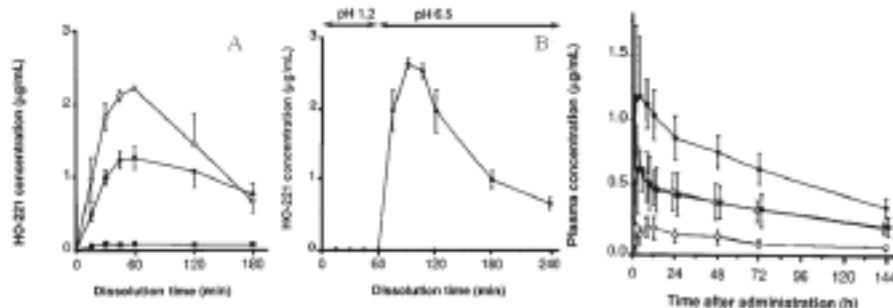
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FIGURE 3



Supersaturated profiles for hydrophilic coprecipitates at pH 6.5 (A), enteric coprecipitates under modified pH-change conditions (B), and in vivo plasma profiles measured in beagle dogs (C). Legend: (○) HP-55, (■) PVP, (□) copolyvidone, and (○) micronized HO-221. Reprinted with permission from reference 12.

vessel is three to five times less than that required to saturate the media within the vessel.⁴ By operating under these conditions, it ensures a sufficient driving force for drug release throughout the testing phase in order to mimic conditions found in vivo during the dissolution and absorption process. Additionally, operating under sink conditions allows for convenient mathematical assumptions facilitating modeling of the release process. Furthermore, traditionally manufactured crystalline dosage forms lack the requisite thermodynamic and kinetic forces for supersaturation, eliminating the need for examination under these conditions. Solid dispersions are capable of supersaturating their environment, necessitating testing under these conditions. Typically, supersaturated dissolution testing is conducted under similar conditions to sink testing; however, the amount of drug added to the vessel is several-fold the amount required for saturation of the media, allowing the formulation (provided it has the underlying properties) to supersaturate the media. Additionally, due to the presence of small particle precipitation, which may occur during the testing period, filter sizes are frequently smaller than those used under sink conditions. It is generally assumed that the particle size

cut-off for cellular uptake is 200 nm, so frequently 0.2-micron PVDF or PTFE filters are employed to reduce crystallization on the filter membrane while minimizing particle size. Utilizing this testing procedure, it becomes possible to ascertain the dissolution rate kinetics associated with a formulation, as well as its ability to provide and maintain supersaturation over prolonged periods of time. In the following sections, examples of in vitro supersaturation are presented along with the resulting enhancement in bioavailability to illustrate the utility of solid dispersions and supersaturation for enhanced therapeutic performance.

IMMEDIATE-RELEASE SUPERSATURATION FROM HYDROPHILIC CARRIERS

According to the BCS, class II compositions exhibit solubility limited to bioavailability, making both the compositional equilibrium solubility and the rate at which it is achieved restrictive steps in the oral absorption process. In order to improve the bioavailability of these drugs, many formulations (both investigative and commercial) have been developed to provide

enhanced dissolution rates. By formulating the solid dispersion with hydrophilic excipients capable of rapid dissolution rates, the drug dissolution rate will become a function of the dissolution rate of the carrier polymer, allowing for enhanced dissolution rates and the potential for supersaturation. Several commonly used materials for this application include hydroxypropylmethylcellulose (HPMC), polyvinylpyrrolidone (PVP), low molecular weight polyethylene glycol (PEG), polyvinylpyrrolidone vinylacetate (PVPVA), and Eudragit® E100. Numerous publications are available in the literature focusing on the dissolution rate enhancement resulting from novel solid dispersion formulations to provide improved bioavailability or faster onset of action; however, only a paucity of these papers examined the ability of these compositions to supersaturate and correlated this behavior to performance in an animal model. In recent years, the importance of supersaturation in achieving improved bioavailability has emerged as a critical design factor for formulation development.

Tacrolimus, which is currently marketed under the trade name Prograf®, is produced as a solid dispersion using a dichloromethane solvent-based coating process. Yamashita et al examined the potential of producing solid dispersions using a thermal processing technique using hydrophilic excipients, including HPMC, PVP, and PEG.¹⁰ In vitro results exhibited substantial supersaturation similar to those produced by compositions using the solvent-based production process. These results were well correlated with in vivo plasma levels measured in cynomolgus monkeys, which showed similar pharmacokinetic profiles between formulations produced using the two manufacturing processes and a substantial improvement over unprocessed crystalline tacrolimus (Figure 1).

Similar approaches have also been described to develop compositions for

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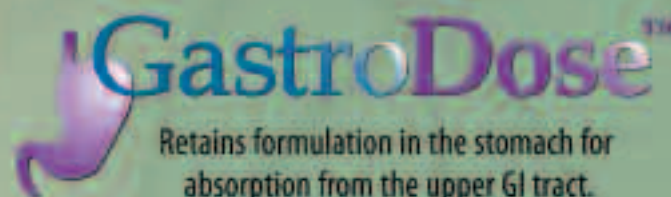
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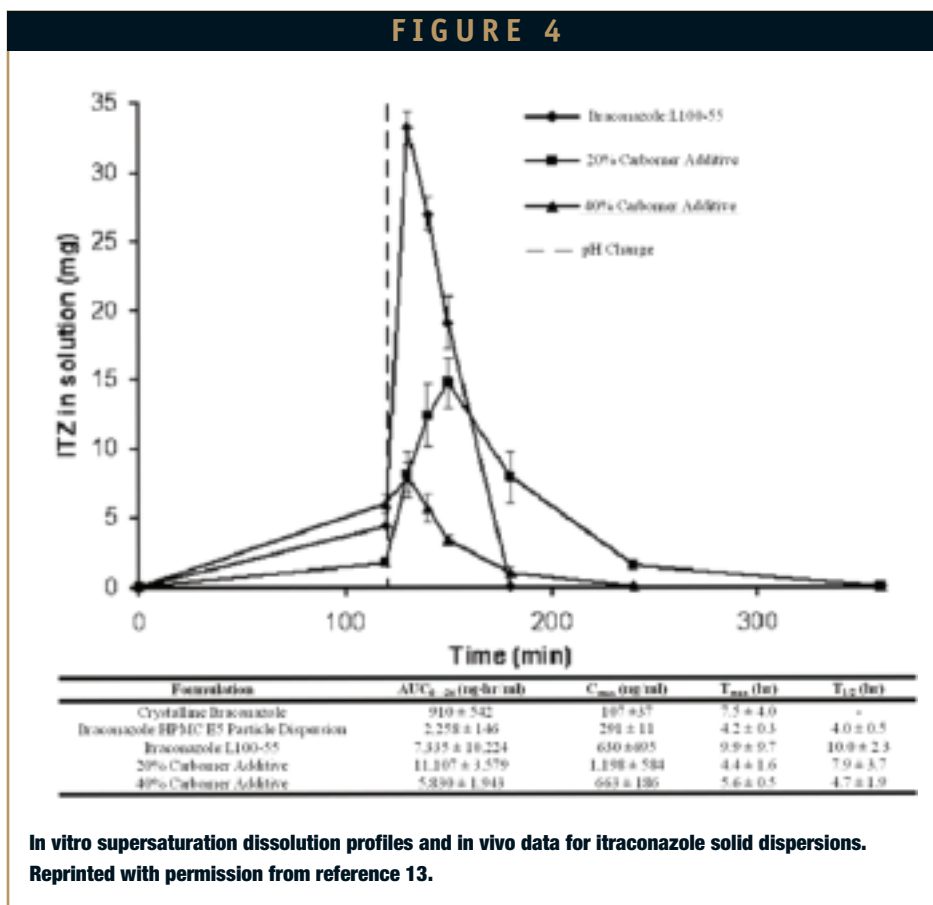
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improved bioavailability of other currently marketed solid dispersions as well. Six et al investigated the ability to produce solid dispersions of itraconazole and several hydrophilic excipients using hot-melt extrusion, characterizing compositions for in vitro dissolution behavior and in vivo pharmacokinetic performance in healthy male volunteers.¹¹ Dissolution testing was conducted under non-sink conditions (equilibrium solubility of itraconazole = 4 to 12 µg/ml) by placing 100-mg itraconazole capsules in 500 ml of simulated gastric fluid without pepsin and conducting testing at 100 rpm. All compositions provided substantial levels of supersaturation; however, the commercial formulation exhibited the slowest dissolution rate (Figure 2).

Surprisingly, pharmacokinetic data generated in human trials showed that HPMC-based compositions provided the greatest AUCs compared to formulations of Eudragit E 100-PVPVA and Eudragit E 100; however, substantial inter-subject variability was observed in all groups. Additionally, similar C_{max} and T_{max} values were observed in vivo, which contradicts what one would anticipate from the in vitro data. The in vivo performance of itraconazole formulations were most likely strongly affected by the solubility properties of itraconazole, which exhibits orders of magnitude lower solubility in more neutral conditions similar to those observed in the upper small intestine, making it an interesting model drug for other advanced solid dispersion technologies, such as site-specific supersaturation and stabilized supersaturation using concentration-enhancing polymers.

SITE-TARGETED SUPERSATURATION USING MODIFIED-RELEASE POLYMERS

While the enhancement in dissolution rate can provide improved oral bioavailability by achieving the equilibrium solubility faster or providing higher metastable equilibrium



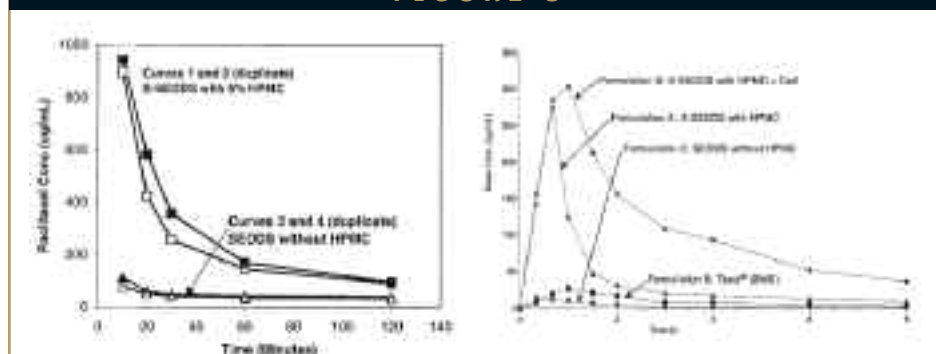
solubility values, these formulations may not provide the greatest improvement in bioavailability. Weakly basic drugs may be ionized at gastric pH where hydrophilic compositions will dissolve and release the drug. Upon transition to the upper small intestine, the pH rises, and the drug may become partially or completely unionized, resulting in a rapid precipitation of dissolved drug. Furthermore, most drugs are primarily absorbed in the upper small intestine, where the substantial surface area provided by the villi and microvilli facilitate transport across the membrane. Compositions that supersaturate the gastric environment for short durations may also be subject to partial or complete precipitation, achieving only equilibrium solubility prior to entering the upper small intestine and negating the tremendous advantages provided by solid

dispersions. In these cases, it would be prudent to target supersaturation to the upper small intestine, which is commonly achieved by using pH-responsive carriers. These carrier materials are insoluble at gastric pH; however, upon entering the upper small intestine, the pH change will trigger ionization of the carboxylic acid functional groups on the polymer chain, resulting in dissolution. As with the hydrophilic solid dispersions, correct formulation and processing can produce compositions whose dissolution rate is governed by that of the polymeric material, resulting in significantly improved dissolution rates, supersaturation, and enhanced bioavailability.

Although a less commonly reported technique for the production of solid dispersions, the use of enteric carriers has been reported to improve bioavailability for at

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FIGURE 5



In vitro supersaturation dissolution profiles and in vivo plasma profiles for paclitaxel formulations developed by Gao et al. Reprinted with permission from reference 15.

least 20 years. In the development of HO-221, a novel anticancer agent, Kondo et al reported the use of micronization technology to enhance the oral bioavailability of the drug in mice, dogs, and monkeys.¹² Their results showed that the production of submicron particles provided modest improvement in bioavailability (~20% BA), although still incomplete. Additionally, a substantial food effect was observed indicating a potential partial solubilization due to bile salts. This group further investigated the use of solid dispersions of hydrophilic and enteric polymers produced by a coprecipitation process for enhanced oral bioavailability (Figure 3). Using hydroxypropylmethylcellulose phthalate (HP-55), in vitro supersaturated dissolution testing conducted at pH 6.5 and with a modified pH-change method showed significant levels of supersaturation. Compositions produced using hydrophilic excipients also achieved substantial levels of supersaturation; however, these systems exhibited precipitation after 60 minutes, which reduced levels of drug in solution during the later stages of testing. In vivo studies in beagle dogs revealed a substantial improvement in bioavailability of the solid dispersions compared to micronized drug, with hydrophilic compositions providing approximately 60% bioavailability and enteric compositions providing nearly complete

bioavailability. The researchers hypothesized that the improvement in oral bioavailability of the enteric compositions was due to the site-targeting of drug release to the upper small intestine, where the drug had been previously shown to be primarily absorbed.

Using a similar approach, Miller and co-workers formulated solid dispersions of itraconazole with Eudragit L100-55 and Carbopol 974P, a mucoadhesive agent.¹³ Because itraconazole is a weakly basic agent having a pKa of ~3.7, it is ionized at acidic pH but exhibits a rapid decrease in apparent solubility at pH values representative of the upper small intestine. By formulating compositions capable of site-specific supersaturation with high-viscosity stabilizers, it was hypothesized that in vivo bioavailability could be improved over traditional hydrophilic solid dispersions of itraconazole. Analytical characterization showed that the amorphous enteric compositions were capable of supersaturation; however, the maximum concentration achieved in vitro decreased with increasing levels of Carbopol (Figure 4). This was attributed to the high viscosity of the polymer, acting to slow the dissolution rate upon pH change. Incorporation of Carbopol 974P at a 20% polymer loading also exhibited the longest duration of in vitro supersaturation via a combination of hydrogen-bonding interactions and high-viscosity stabilization.

In vivo testing in Sprague-Dawley rats demonstrated that the composition containing 20% Carbopol 974P also provided the greatest AUC, suggesting that the maximum concentration achieved was secondary to the ability to maintain supersaturation for physiologically relevant time scales. Furthermore, the high variability of the itraconazole:L100-55 composition observed in vivo was attributed to the inability to stabilize supersaturation, highlighting the importance of maintaining supersaturation for enhanced performance.

CONCENTRATION-ENHANCING POLYMERS FOR PROLONGED DURATIONS OF SUPERSATURATION

The importance of maintaining levels of supersaturation has been clearly illustrated in the previous examples in which decreasing levels of solubilized drug can result in incomplete and highly variable bioavailability. By developing formulations with materials capable of inhibiting precipitation from supersaturation, termed concentration enhancing polymers, it is possible to improve the bioavailability of poorly water-soluble compounds. Concentration-enhancing polymers provide increased levels of drug in solution in excess of the normal equilibrium solubility through either physical, chemical, or a combination thereof of interactions with drug molecules that inhibits precipitation.¹⁴ Using these materials, several formulations have demonstrated substantial improvements in oral bioavailability.

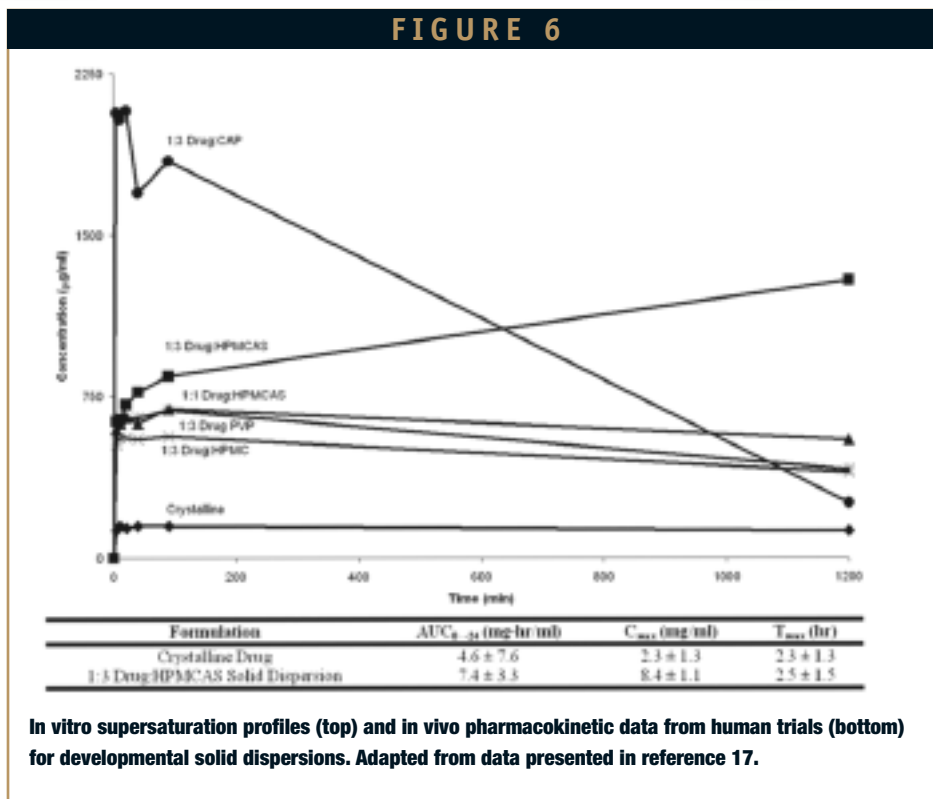
Although not studied for solid dispersions, Gao and co-workers developed supersaturatable self-emulsifying drug delivery systems (s-SEDSS) utilizing concentration-enhancing polymers for the delivery of paclitaxel and an experimental compound PNU-91325.^{15,16} In these studies, s-SEDSS compositions containing HPMC E5

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as a concentration-enhancing polymer were developed to provide drug supersaturation and precipitation inhibition. Results from both studies showed substantial inhibition of precipitation, with HPMC levels of 5% providing significantly longer durations of paclitaxel supersaturation. When in vivo performance of paclitaxel s-SEDDS formulations was assessed in vitro and in a rat model, oral bioavailability increased from 0.9% in conventional SEDDS compositions to 9.5% through the use of HPMC as a concentration-enhancing polymer (Figure 5). An additional increase in oral bioavailability was achieved when co-administered with cyclosporine A, most likely due to its inhibitory effects of CYP3A4.

Concentration-enhancing polymers have also been applied to solid dispersion formulations. In a recent patent, the use of these materials in formulating compositions of a low-solubility glycogen phosphorylase inhibitor were detailed.¹⁷ Amorphous compositions of the drug were prepared by spray-drying using a variety of excipients, including HPMC, PVP, hydroxypropyl methylcellulose acetate succinate (HPMCAS), and cellulose acetate phthalate (CAP). In vitro supersaturated dissolution testing was conducted to assess the performance of these materials by adding excess material to dissolution vessels containing a phosphate buffer solution having a pH of 6.5. Testing showed that spray-dried powders containing CAP produced the greatest magnitude of supersaturation; however, precipitation was observed. Compositions of HPMCAS showed the greatest level of stabilization with no decrease in concentration observed for compositions of the 1:3 drug:polymer ratio (Figure 6). In vivo testing of this composition as an orally administered powder showed a significant increase in bioavailability compared to the crystalline drug, which can be attributed to the substantial in vitro AUC observed during testing.

Oral bioavailability improvement of



itraconazole has also been achieved using this concept. In a recent study by DiNunzio et al, solid dispersion engineered particles of itraconazole were produced by ultra-rapid freezing (URF) using enteric polymers, characterized for in vitro dissolution performance using a pH-change method and compared to the commercially available multiparticulate solid-dispersion formulation in a rat model.¹⁴ The compositions produced using URF were shown to be amorphous and exhibited a significant specific surface area. Although both compositions were shown to be amorphous, compositions containing CAP as the carrier showed a substantially greater degree of supersaturation compared to compositions using polyvinyl acetate phthalate (PVAP). Furthermore, compositions containing CAP showed a much greater ability to stabilize itraconazole in a supersaturated state. The difference in stabilization properties was attributed to steric hindrance and increased polymeric rigidity of

the CAP backbone compared to PVAP. When compared to Sporanox® pellets dosed at the same strength, a nearly two-fold increase in oral bioavailability was observed demonstrating the utility of concentration-enhancing polymers for improving oral bioavailability.

SUMMARY

With the increasing number of poorly water-soluble compounds in developmental portfolios, the importance of supersaturatable compositions will continue to grow. Throughout the past several decades, solid dispersions capable of achieving supersaturation have emerged as a viable technology to address the ever-expanding number of poorly water-soluble drugs through kinetic and thermodynamic mechanisms of solubility enhancement. Formulation of these compositions with hydrophilic polymers has

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been shown to be a highly effective way for improving the bioavailability and onset of action for a number of compounds. Additionally, the use of enteric polymers and concentration-enhancing polymers have been shown to enhance bioavailability by more effectively targeting and maintaining supersaturation at the site of absorption. Using these formulation techniques for the development of poorly water-soluble compounds will continue to be an effective way of enhancing product bioavailability.

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BIOGRAPHIES



Mr. James C. DiNunzio is currently a graduate student in the Division of Pharmaceutics at The University of Texas at Austin. Prior to entering the PhD program, he spent 3 years working as a Scientist in the Pharmaceutical Technology & Development Group at Forest Laboratories, where his responsibilities included supervising scale-up, process optimization, and clinical trial manufacturing activities for developmental products. He earned his MS in Chemical Engineering from Columbia University and his BS (cum laude with distinction) in Chemical Engineering from the State University of New York at Buffalo.



Dr. Dave A. Miller is a Research Scientist in the Pharmaceutical and Analytical Research and Development department at Hoffmann-La Roche Inc. in Nutley, NJ. He earned his BS in Chemical Engineering (2002) and his PhD in Pharmaceutics (2007) from the University of Texas at Austin. Dr. Miller's primary research interests involve advanced formulation and process technologies aimed at improving the oral absorption of poorly water-soluble drugs. His research in this area has produced several publications and two pending patents. He has also published in the areas of polymeric film coating, sustained-release technologies, and dissolution testing methodologies.



Dr. James W. McGinity is the holder of the Johnson and Johnson Centennial Chair in Pharmacy and is Professor of Pharmaceutics in the College of Pharmacy, The University of Texas at Austin. He earned his BS in Pharmacy at the University of Queensland, Australia, and his PhD in Pharmaceutics from the University of Iowa. Prior to joining The University of Texas at Austin, he was a Research Scientist at the Squibb Institute for Medical Research in New Brunswick, NJ. Dr. McGinity's research interests and publications are in the areas of pharmaceutical technology and novel drug delivery systems. He has been issued 23 US patents.

His present research interests center on solid dosage forms, aqueous film coating of pellets and tablets, powder technology, materials science, and hot-melt extrusion. He has been the USA Editor for the *European Journal of Pharmaceutics and Biopharmaceutics* since 1995 and an charter Editorial Advisory Board member for *Drug Delivery Technology* since 2001. Dr. McGinity has participated in several national and international scientific symposia and conferences. He has been a consultant to the FDA and to many pharmaceutical and chemical companies both in the US and Europe. He is an AAPS Fellow and was the recipient of the 1999 Pharmaceutical Preparation and Particle Design (PPD) Award presented by the Society of Powder Technology Japan and more recently, the Takeru & Aya Higuchi Award (2004) and the AAPS 2005 Research Achievement Award in Pharmaceutical Technology.



Dr. Robert O. Williams III is the Johnson & Johnson Centennial Professor and Division Head of Pharmaceutics at the College of Pharmacy, University of Texas at Austin. He earned his BS in Biology from Texas A&M University, a BS in Pharmacy from the University of Texas at Austin, and Doctor of Philosophy in Pharmaceutics in 1986 from the University of Texas at Austin. Dr. Williams worked 9 years in the pharmaceutical industry in the US and France before returning to the University of Texas at Austin. He was elected a Fellow of the AAPS in 2006 and a Fellow of the American Institute of Medical and Biological Engineering in 2008. Dr. Williams is a member of the AACP, AAPS, ACS, Association de Pharmacie Galénique Industrielle, CRS, and European Federation of Biotechnology. He was the Co-founder and President of PharmaForm LLC from 1996 to 2007, and is a Director of Akela Pharma, Inc. Dr. Williams' research interests include development of novel drug delivery systems for oral, pulmonary, nasal, injectable, buccal and topical applications; development of novel particle engineering technologies for low molecular weight drugs, peptides, and proteins; and analytical technologies to characterize actives, excipients, and polymers. He has published over 250 articles, abstracts, and book chapters in the fields of pharmaceutical technology and drug delivery. He is an inventor on several patents and patent applications. Dr. Williams is the Editor-in-Chief of the research journal *Drug Development and Industrial Pharmacy*.

TRANSDERMAL DELIVERY

Transdermal Delivery of Various Molecules In Vivo Using Alpha-tocopheryl Phosphate

By: Paul Gavin, PhD; Annike Griffey, Robert Gianello, PhD; Nicholas Kennedy, PhD; Hooi-Hong Keah, PhD; Jeremy Cottrell, PhD; and Esra Ogru, PhD

INTRODUCTION

Transdermal drug delivery has the potential to reduce side effects, localize delivery, increase patient compliance, and help circumvent first-pass hepatic clearance of drugs. However, while the potential benefits of transdermal drug delivery are enormous, in reality, the range of drugs that pass effectively through the skin is limited. Most drugs require the use of chemical agents to improve delivery, or administration systems that involve direct perturbation, or bypassing of, the strata corneum/epidermis. These methods are often associated with irritation, inconvenient equipment, or monetary expense. The Holy Grail for transdermal drug delivery remains a non-invasive delivery platform, able to cheaply, discretely, and conveniently administer therapeutic levels of a range of drugs, with little to no irritation. This is not a simple task considering that skin evolved over millions of years into a highly effective barrier that prevents the ingress of foreign molecules.

Vitamin E (alpha-tocopherol; tocopherol) is the most common lipid-soluble anti-oxidant in humans, and is a key biological component of all membranes.¹ In addition to the importance of cellular tocopherol throughout the body, evidence demonstrates its particular importance in the skin. Sustained dietary intake of tocopherol elevates its levels in the epidermis, where it provides protection against oxidative stress caused by

exposure to UV radiation.² Direct topical application of tocopherol provides a number of benefits, including protection against UV-induced oxidative stress, skin carcinogenesis, and erythema.³⁻⁵ Interestingly, tocopherol also acts as a penetration enhancer for transdermal absorption.⁶

Phosphagenics has recently demonstrated the existence of the natural phosphorylated form of vitamin E, alpha-tocopheryl phosphate (TP), in a variety of organs within the body.⁷ Given the ability of alpha-tocopherol to enhance transdermal penetration, we sought to investigate whether TP also enables the transdermal delivery of drugs of interest. Experiments conducted in the laboratory demonstrated that topically applied formulations containing a mixture of

alpha-tocopheryl phosphates (TPM) and either coenzyme Q (CoQ), morphine, oxycodone, or insulin increased drug passage into and through the skin. Individually and collectively, these results demonstrate that formulations containing TPM are effective in transporting a diverse range of drugs dermally and transdermally in concentrations sufficient to result in a therapeutic effect. Therefore, the TPM delivery platform has significant potential to expand the number and types of drugs available for topical application and transdermal delivery.

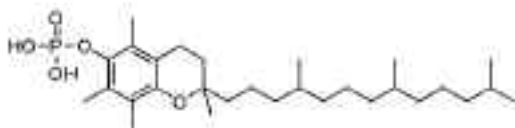
TPM METHODOLOGY

The following studies report our efforts to deliver a range of different

FIGURE 1

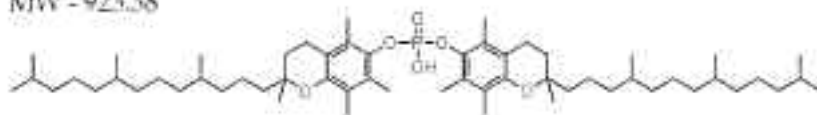
α -Tocopheryl phosphate (TP)

$C_{29}H_{50}O_5P$
MW - 510.69



Di- α -tocopheryl phosphate (T₂P)

$C_{58}H_{100}O_{10}P_2$
MW - 923.38



Chemical Structures of the Phosphorylated Tocopherols

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molecules using the TPM delivery platform. TPM is a mixture of alpha-tocopheryl phosphate and di-alpha-tocopheryl phosphate (Figure 1). CoQ₁₀, morphine, oxycodone, and insulin were all formulated with TPM. The resulting formulations, TPM/CoQ, TPM/Morphine, TPM/Oxycodone, and TPM/insulin, were compared against suitable control formulations in rat studies in order to gain information on the in vivo drug delivery. For all studies, Sprague-Dawley rats were anaesthetized and prepared for experiments by shaving an area ~ 5 x 4 cm from the back. All TPM formulations were applied topically and massaged into the skin the day after shaving. Experimental parameters pertaining to each drug are described further.

CO-ENZYME Q₁₀

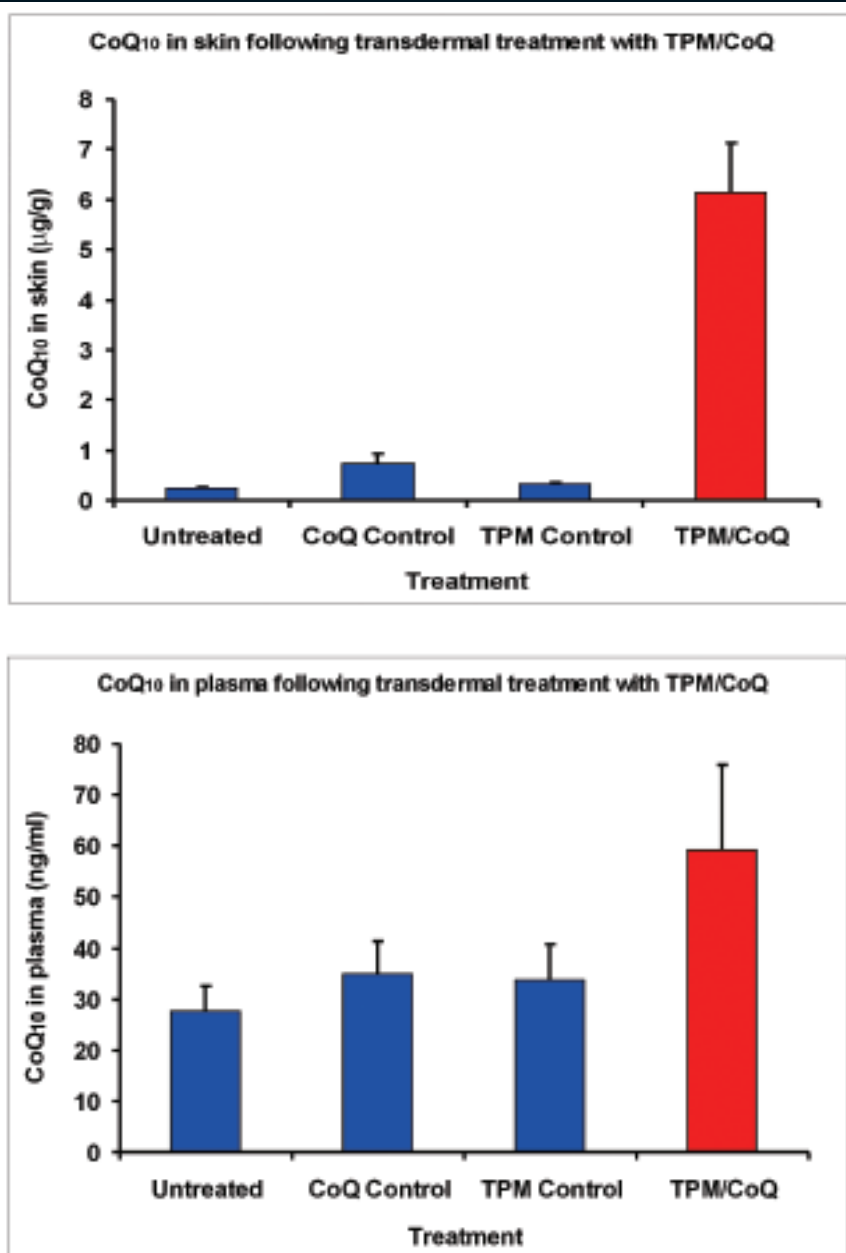
Co-Enzyme Q₁₀ (CoQ₁₀, ubiquinone-10) is a fat-soluble, vitamin-like nutrient existing in all cellular membranes.⁸ It is essential for cell respiration and electron transfer, and its reduced form (ubiquinol) has antioxidant functions similar to vitamin E.⁹ Within the skin, CoQ₁₀ protects against UV exposure and is able to regenerate tocopherol from its UV-produced radicals.¹⁰ These functions have made CoQ₁₀ particularly attractive to the cosmetic industry in that it protects against environmental insult, photoaging, and regenerates tocopherol.

Rats (n = 6) were treated with TPM/CoQ (5 mg/kg CoQ) and control formulations (TPM alone or 5 mg/kg CoQ₁₀ alone). The following day, rats were euthanized, and plasma and washed skin was extracted for quantification via HPLC.¹¹ Application of TPM/CoQ to the dorsal region of rats produced a significant (p < 0.05) increase in the amount of CoQ₁₀ present within plasma and skin. Twenty four

hours after application, mean CoQ₁₀ levels in skin (Figure 2A) were increased by 2491%, 733%, and 1830% relative to the untreated, CoQ control (lacking TPM) and TPM control (lacking CoQ), respectively. Mean CoQ₁₀ levels in plasma (Figure 2B)

were also increased by 115%, 70%, and 76% relative to the untreated, CoQ and TPM controls, respectively. Collectively, these data demonstrate TPM increased dermal and transdermal uptake of CoQ₁₀.

FIGURES 2A & 2B



Increased Levels of CoQ₁₀ in Plasma & Skin Following Transdermal Application of TPM/CoQ

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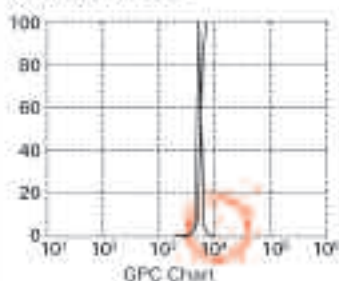
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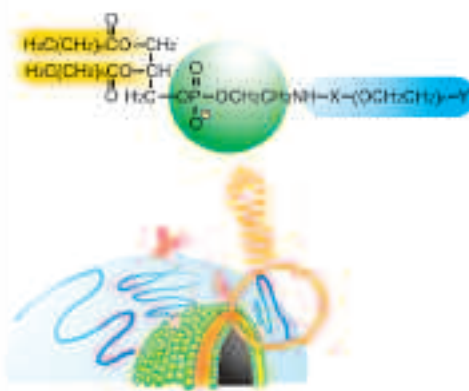
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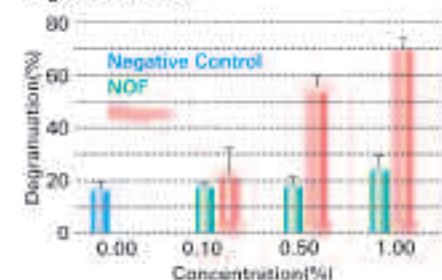
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MORPHINE

The ability to deliver morphine through the skin has the potential to improve quality of life and pain management. This is because the present methods of delivering morphine (oral, suppository, or injection) can also

result in adverse side effects, such as blurred vision, constipation, and central nervous system disturbances. The ability to deliver localized, peripheral doses of morphine to target tissues through the skin may reduce some of the side effects.

Paw withdrawal latency after a heat

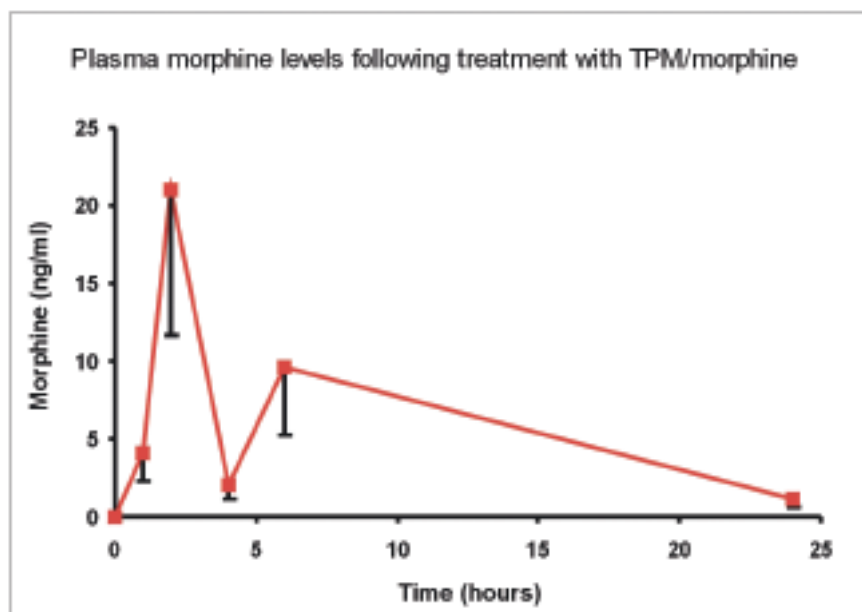
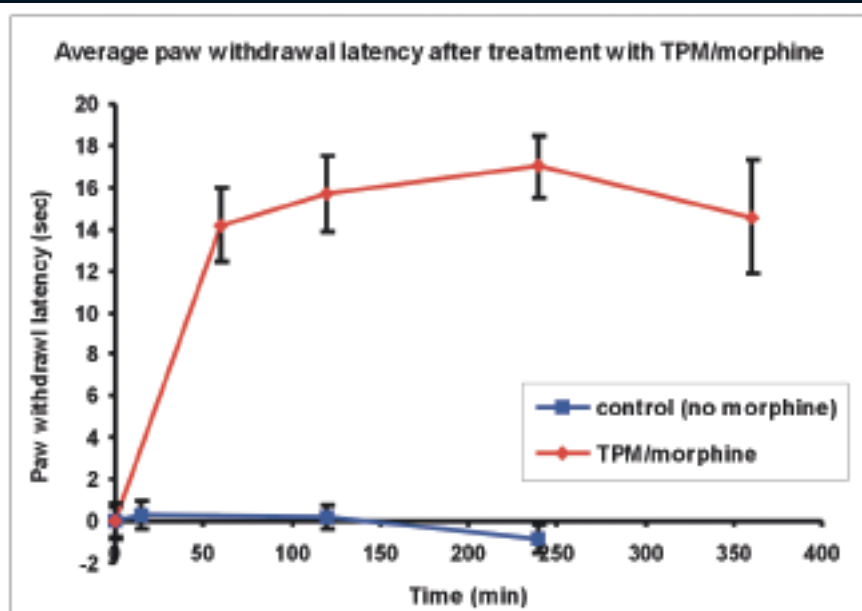
stimulus was used as a measure of morphine-induced analgesia, using a plantar analgesiometer after a single dose (1.6 mg/kg). Each rat ($n = 6$) was placed in a rectangular box (0.3 x 0.2 m) with a clear plastic floor in which the rat was free to move about. An infrared light source located beneath the chamber was positioned under a hind paw. Once activated, infrared heat was emitted and focused on the paw, which heated the skin up to $\sim 45^{\circ}\text{C}$. The rat's reaction in moving its paw away from the heat source triggered a recording of the paw withdrawal time. Analgesia was tested at selected time-points after a single administration of control or TPM/morphine formulations (approx 5 mg morphine/kg body weight). Rats were tested three times at each time point. The latency of the zero-time points were averaged and subtracted from all subsequent latencies.

TPM/morphine increased paw withdrawal latency by 14 to 16 seconds between 1 and 6 hours, indicating significant morphine-induced analgesia ($p < 0.05$, Figure 3A). Strong analgesic effects have been observed up to 48 hours after administration of TPM/morphine (data not shown). Plasma morphine concentrations collected from euthanized rats showed that morphine concentrations peaked at approximately 20 ng/mL, 2 hours after application (Figure 3B).

OXYCODONE

Oxycodone is the leading opioid in clinical use in the United States. Although the analgesic effects of oxycodone are very similar to morphine, oxycodone has a rapid onset of action, and its oral bioavailability is approximately twice that of morphine. Although oxycodone is available exclusively as oral formulations, alternative routes of administration, such as intramuscular, intranasal, subcutaneous, and rectal, have

FIGURES 3A & 3B



Analgesia & Plasma Morphine Concentration Following Transdermal Application of TPM/Morphine

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been investigated. To date however, oxycodone has not been administered via the topical (dermal) route.

The pharmacokinetics of topically applied TPM/Oxycodone gel (approx 5 mg oxycodone/kg body weight) versus positive control (oxycodone, water) was determined in rats ($n = 6/\text{treatment group}$). Rats were dosed twice daily with their treatment (AM and PM, approx 10:00 hours and 15:00 hours) for 3 days and a single dose on day 4 (AM dose only). From this, it was observed that TPM/Oxycodone significantly increased plasma oxycodone concentrations compared to the positive control, indicating TPM enhanced transdermal permeation of oxycodone in rats (Figure 4A).

As observed with morphine, the increased concentrations of oxycodone delivered transdermally resulted in analgesia, as measured by longer paw withdrawal latencies (Figure 4B). TPM/Oxycodone-mediated analgesia (10 mg oxycodone/kg) was approximately 12 seconds longer than TPM and oxycodone positive control (10 mg oxycodone/kg), indicating that TPM increases skin permeation of topically applied oxycodone. TPM/Oxycodone-mediated analgesia was equivalent to 3 mg/kg IP oxycodone, but was longer lasting. Combined, these data demonstrate that TPM formulations increase the permeation of oxycodone through the skin in concentrations sufficient to have a therapeutic effect. Furthermore, a single dose of TPM/Oxycodone results in prolonged duration of action, lasting at least 6 hours in rats.

INSULIN

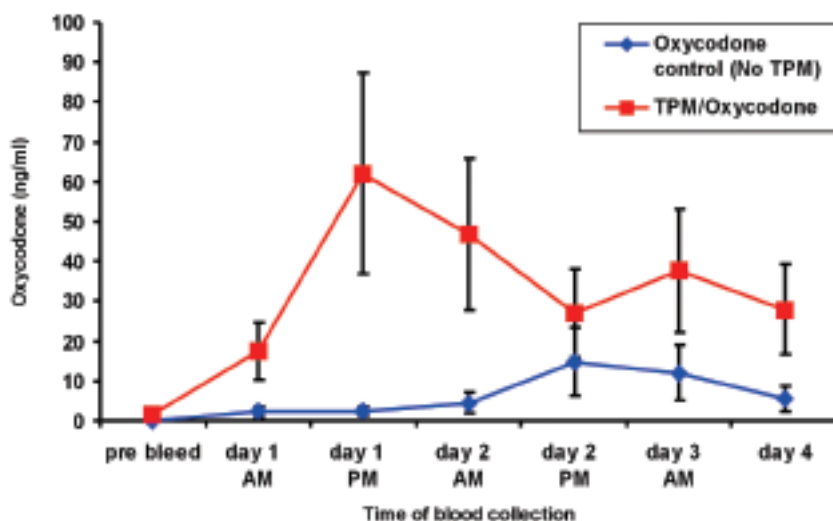
Currently, the only means of insulin treatment is via daily injection, which can be a significant burden for people with diabetes. Insulin therefore represents a very attractive target for transdermal delivery.

However, due to the relatively large size and charged nature of most peptides and proteins (insulin ~ 6 kDa), the efficacy in passive transdermal delivery is extremely poor. Systems involving electric current, such as iontophoresis and electroporation,

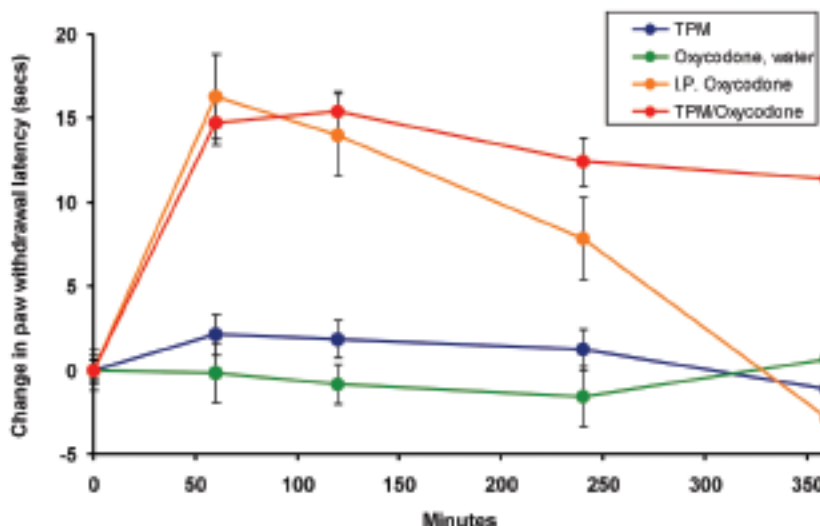
can drive such molecules across the stratum corneum and are beginning to show promise for insulin delivery.¹²⁻¹⁶ We sought to investigate whether the penetration-enhancing effects of TPM would facilitate the passive transdermal delivery of a large

FIGURES 4A & 4B

Plasma Oxycodone concentration following topical application of TPM/Oxycodone



Change in paw withdrawal following topical application of TPM/Oxycodone



Plasma Oxycodone Concentration & Analgesia Following Transdermal Application of TPM/Oxycodone

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molecule like insulin.

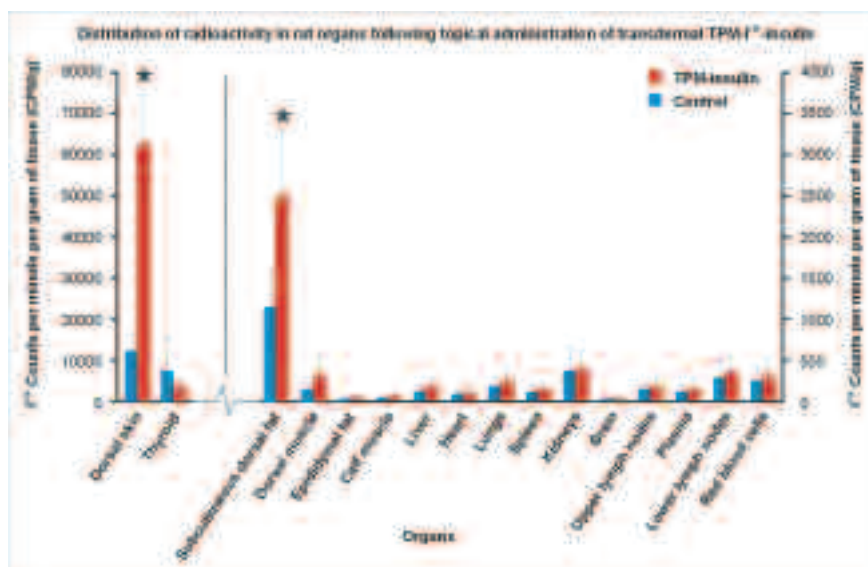
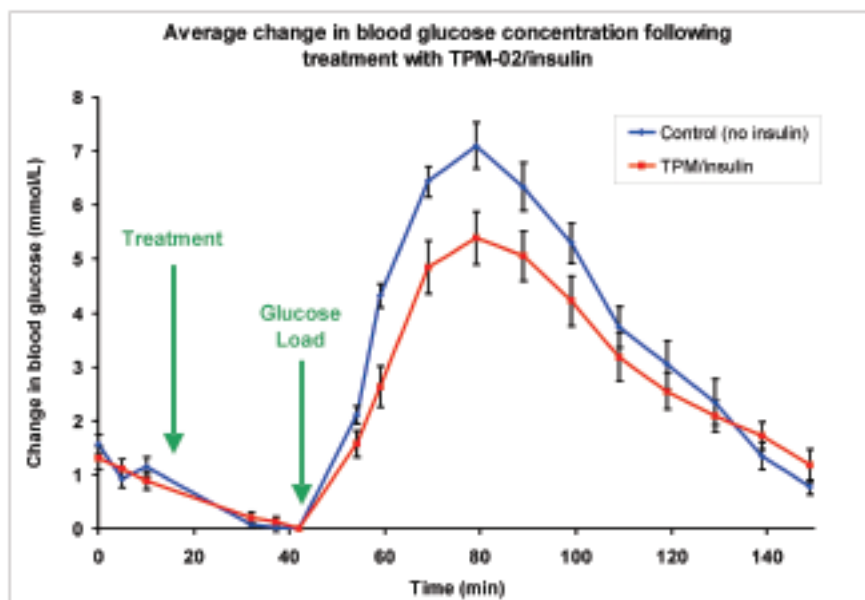
Healthy rats shaved on the back were fasted overnight and subjected to a glucose

tolerance test (IP; 2g/kg body weight) the following morning under anesthesia. Rats treated with TPM/insulin (n = 15) received

topical application of TPM/insulin (32.5 U/kg body weight) 30 minutes prior to the glucose load to allow the insulin time to permeate the skin and enter systemic circulation. Rats were maintained under anesthesia and blood glucose measured by tail bleeding every 10 minutes. The average change (from baseline) in blood glucose was calculated for each time-point and plotted. The successful transdermal delivery of insulin was confirmed by formulating TPM with ^{125}I -insulin. TPM/ ^{125}I -insulin was applied as per previous studies, and the rats were euthanized 4 hours later. The skin was washed with distilled H_2O , and the organs were harvested before gamma-counting.

Mean blood glucose levels following treatment with TPM/insulin are summarized in Figure 5A. Peak blood glucose levels following IP glucose load were reduced by ~2 mmol/L after pretreatment with TPM/insulin, indicating successful transdermal delivery of insulin. Statistical analysis of the area under the curve showed this reduction to be significant ($p < 0.05$). Significant levels of the I^{125} -radiolabel could be detected in both the skin ($p < 0.001$) and subcutaneous fat ($p < 0.05$), indicating deep penetration of the dermal layers (Figure 5B).

FIGURES 5A & 5B



Decreased Blood Glucose & Distribution of I^{125} -Insulin Following Transdermal Application of TPM/insulin

CONCLUSION

The potent transdermal properties of TPM were able to drive the absorption of CoQ_{10} , morphine, oxycodone, and insulin across the skin despite their wide variety in chemical composition. The TPM delivery platform has great potential for the topical application and absorption of a variety of molecules known to have poor oral bioavailability or side effects that manifest after absorption.

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BIOGRAPHIES



Dr. Paul Gavin is a Senior Research Fellow managing the Formulation group at Phosphagenics. He is responsible for the research and development of Phosphagenics' patented TPM delivery platform. Dr. Gavin earned his PhD in Biochemistry at Monash University, Melbourne, specializing in the structural assembly of enzymes and bioenergetics. He has been with Phosphagenics since 2002.

Ms. Annike Griffey is a Research Assistant in the Formulation group at Phosphagenics. She is responsible for conducting in vivo testing of topical/transdermal formulations in small animal models. Ms. Griffey earned her BSc at Monash University, with Honours in Biochemistry. She has been with Phosphagenics since 2004.



Dr. Robert Gianello is a Senior Scientist managing the R&D group at Phosphagenics. He is responsible for overseeing research and development within the company. Dr. Gianello earned his PhD at Monash University, Melbourne, focusing on drug discovery, development, and delivery. He has over 25 years experience in biomedical research and has been with Phosphagenics since 2001.



Dr. Nicholas Kennedy is a Research Fellow in the Formulation group at Phosphagenics. He runs the in vitro testing facility responsible for testing Phosphagenics patented transdermal delivery technology. Dr. Kennedy earned his PhD in Biochemistry at Monash University and the Centre of Animal Biotechnology, Melbourne, specializing in DNA vaccines. He has been with Phosphagenics for 2 years.



Dr. Hooi-Hong Keah earned her PhD from the Chemistry Department at Monash University. She currently heads the Bioanalytical Group at Phosphagenics, where she is responsible for sample analysis and method development. Prior to joining Phosphagenics, she was a NHMRC Research Fellow working on various projects mainly in the area of peptide and protein research. Dr. Keah has extensive experience in biomolecules separation using HPLC and LCMS.



Dr. Jeremy Cottrell is a Research Fellow in the Formulation group at Phosphagenics. He is responsible for managing the in vivo testing of topical/transdermal formulations in small and large animal models. Dr. Cottrell earned his PhD in Biochemistry with the Department of Primary Industries, Victoria University, Melbourne, specializing in muscle biochemistry. He completed a Post-doc within the Children's Nutrition Centre at Baylor College of Medicine (Houston) before joining Phosphagenics in 2007.



Dr. Esra Ogru is an Executive Director of Phosphagenics and is responsible for the coordination and management of the preclinical, clinical, and development research in Australia and internationally. Dr. Ogru has many years experience in both the academic and commercial aspects of the industry. Prior to joining Phosphagenics in 2001, she carried out significant research on obesity and diabetes. Additionally, she has considerable experience in the management and coordination of preclinical and clinical development of pharmaceutical products.

GASTROINTESTINAL DELIVERY

BIOROD™: Bioadhesive-Based Oral System for Targeted Delivery

By: Avinash Nangia, PhD

INTRODUCTION

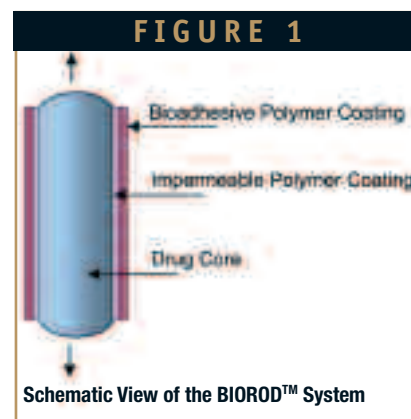
The use of bioadhesive polymers, as a means of delivering therapeutic agents to the gastrointestinal tract (GIT), has been a focus of attention in the past two decades.^{1,2} Bioadhesive oral drug delivery systems exploit the interaction between the mucus and bioadhesive polymers and thus offer significant advantages.^{3,4} Oral delivery systems formulated with bioadhesive polymers may increase GIT residence time leading to improved oral bioavailability, as the formulation will achieve a greater opportunity to interact closely with the absorption site.^{5,6} Bioadhesive polymeric systems may also be useful for coating damaged esophageal and intestinal wall tissues, and thus defending against various irritants.⁷ The ability to maintain an oral delivery system at the target location for an extended period of time has great appeal for the treatment of both local conditions as well as sustained systemic absorption.⁸⁻¹⁰

The promise of a bioadhesive-based oral delivery system has fostered numerous investigations with limited success.¹¹ Different types of oral delivery systems have been explored utilizing various hydrophilic hydrogel bioadhesive polymers.¹² When these hydrophilic polymers are used for oral bioadhesive systems for delivery of drugs in the GIT, they typically hydrate prematurely upon contact with the stomach contents before developing interactions with the mucosal surface. In the event that some weak interactions do occur, these systems cannot withstand the high turbulence of the stomach environment, and the result is premature emptying. Therefore, while the range of hydrophilic bioadhesive polymers and their application in various low-turbulence conditions is quite broad, their usefulness in oral dosage forms, especially in designing of systems for systemic delivery, is generally limited.

An ideal bioadhesive oral dosage form must meet several prerequisites to be successful. The first prerequisite to target a gastrointestinal site is that the behavior of the dosage form must be reproducible. Although many bioadhesive polymers have exhibited promising results in vitro and in vivo in animals, few benefits have been shown in human trials.

The second prerequisite for a bioadhesive system is that it should rapidly attach to the mucosal surface and maintain a strong interaction to prevent displacement. Spontaneous adhesion of the system at the target site is critical. Contact time should also be sufficiently long at the target site, normally longer than that needed for complete drug release. As hydrophilic bioadhesive polymers tend to lose adhesiveness upon hydration, restricted hydration and formation of a rigid gel network would be desirable for prolonged adhesion.¹³ A short retention time, in relation to the drug release rate, will compromise the bioavailability.

The third prerequisite for a successful and effective bioadhesive system is that the bioadhesion performance should not be impacted by surrounding environmental pH. Studies have shown that the bioadhesiveness of polymers with ionizable groups are affected by surrounding pH. For example, polyacrylic acid is more bioadhesive when the majority of the carboxylic acid groups are in the ionized state. Polyanhydride-based hydrophobic bioadhesive polymers from Spherics (Spheromers™) undergo erosion, which is mainly affected by the aqueous environment and not by pH of the surrounding medium. Studies have shown that as anhydride-based polymers degrade at the mucus surface, carboxylic acid groups are formed at the transected polymer chain ends, which generate a new polymer surface rich in carboxylic acid end groups.¹⁴ These hydrophilic functional groups then form hydrogen bonds with surrounding mucin



strands that in turn penetrate the newly created surfaces. The result is the formation of both chemical and mechanical bonds. As the degradation process proceeds, a more porous surface rich with carboxyl groups is created allowing for even greater adhesion, which is essential to the success of oral bioadhesive systems.

Another prerequisite for an ideal bioadhesive delivery system is that the bioadhesive and drug-release functions are independent of each other. Often, the bioadhesive polymer used in the dosage form is also used to regulate the release of drug. Generally, these formulations are made by mixing bioadhesive polymer and drug or by coating drug-loaded beads or tablets with the bioadhesive polymer. These approaches of using bioadhesive polymers to achieve both bioadhesion and drug-release functions have compromised results.

An effective bioadhesive formulation must not cause local tissue irritation or long-term tissue toxicity due to the bioadhesive polymer or other absorption enhancers that may be used to promote drug absorption. Other desirable characteristics of a bioadhesive dosage form include high-drug loading, complete drug release, and convenient administration.

Based on these desirable attributes, a patented BIOadhesive Rate-controlled Oral Delivery system (BIOROD™) was

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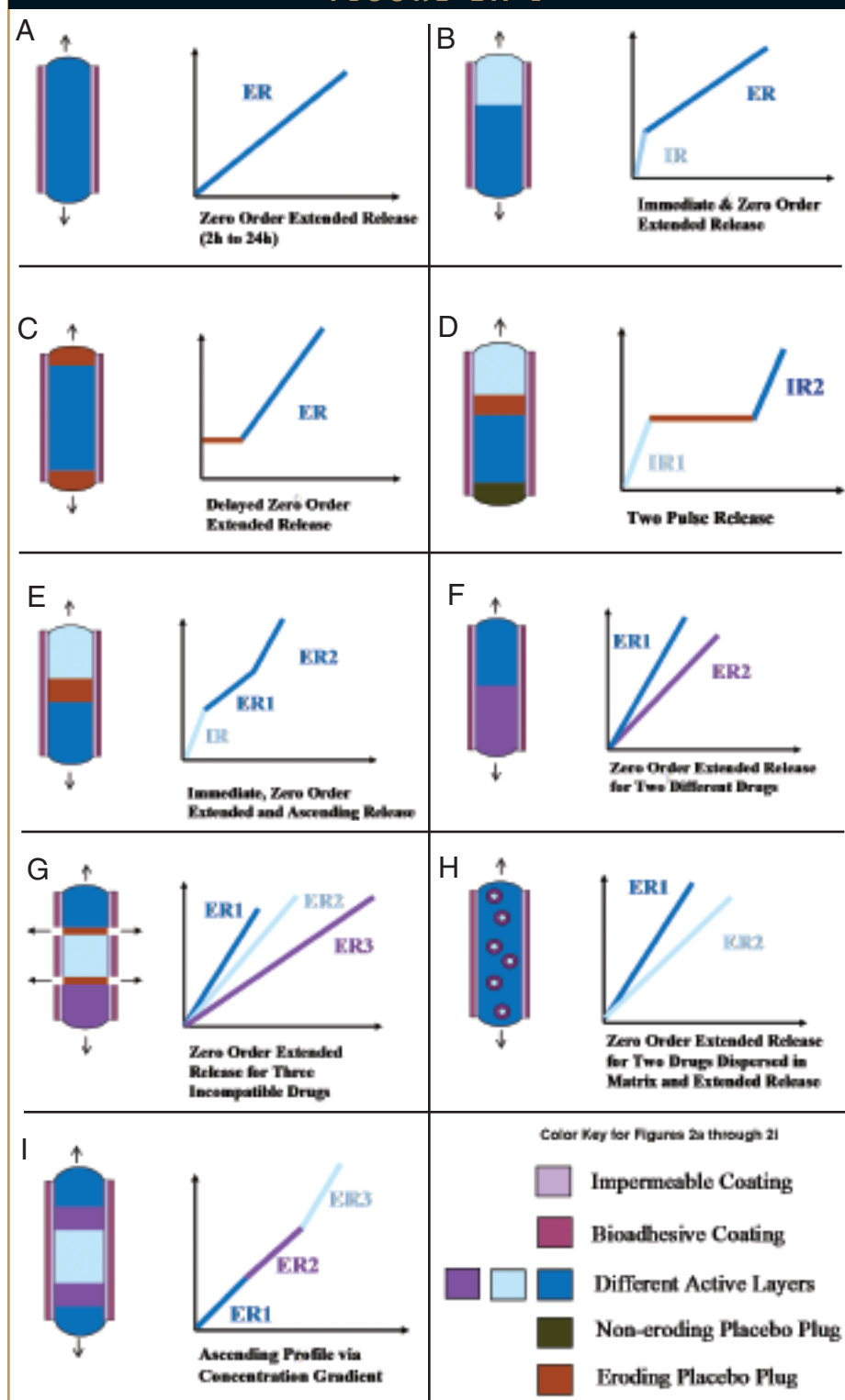
conceptualized at Spherics.¹⁵ BIOROD was conceived on the premise that the system will allow drug(s) to be released at a target GIT absorption site in a controlled and customized manner. Other oral controlled-release dosage forms (eg, OROS®, Geomatrix®, Theriform®, Egalet®) have also shown to deliver customized release profiles.¹⁶⁻¹⁸ However, these systems remain ineffective for drugs with narrow absorption windows. Because these systems cannot retain the drug at the target absorption window, they result in lower than expected bioavailability. Therefore, there remains a need to develop a system that provides both controlled and customized release, as well as retains the drug at its preferred absorption site in the GIT over an extended duration.

BIOROD SYSTEM

The BIOROD system consists of a longitudinally compressed cylindrical tablet (ie, the inner drug core), which is coated with an inner impermeable polymer and an outer bioadhesive polymer (Figure 1). The inner drug core is composed of a controlled-release erodible tablet matrix. The impermeable and bioadhesive polymer coatings encase the inner drug core, except for the two ends of the cylindrical tablet. When the system adheres to the mucosal surface, the release of the drug(s) from the inner core is controlled by erosion, which occurs from either one or both open ends in a reproducible manner. Because the eroding surface area remains constant throughout dissolution, a near zero-order release profile can be achieved. The inner capsule shape core, when compared to standard convex tablet, provides better plug flow, which results in more efficient delivery with no residual drug. When the drug is fully released from the inner core, the remaining hydrated polymeric shell is eliminated intact in the feces. A BIOROD system with an impermeable coating but without the bioadhesive polymer coating is called POLYROD.™

One of the significant advantages of the BIOROD system is the flexibility of designing different drug-release profiles to achieve therapeutic goals. The drug-release profile from the BIOROD system is easily adjusted by the formulation and design of the inner drug core and/or the outer impermeable and bioadhesive

FIGURE 2A-I



Schematics of Various Design Options of the BIOROD™ System

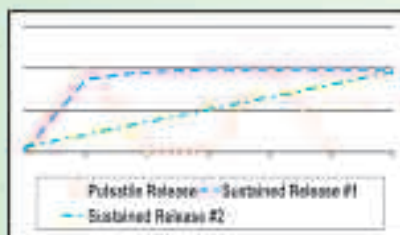
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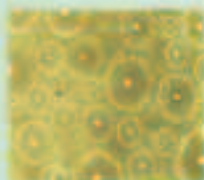
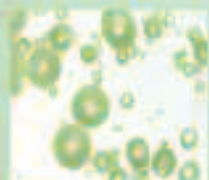


Orally Disintegrating Dosage Forms (ODD)

- Rapid Dissolve tablet forms
- ODT
- Two layer KOR-Koat Tabs
- Healthee Chew Cubes
- Chew Tabs
- Flash Melt Beads



Microencapsulation



Main Encapsulation Process

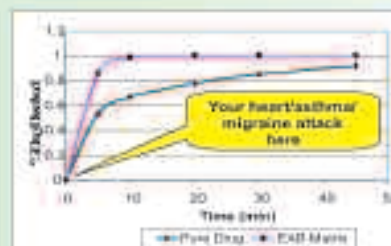
- Coacervation
- Spray Systems
 - Spray Drying
 - Spray Congealing
- Fluidization
 - Polymer Coating
 - Hot Melt Coating
- Adsorption
- Complexation
- Others
 - Extrusion
 - Microemulsions



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GASTROINTESTINAL DELIVERY

TABLE 1

- Applicable to Both Soluble & Insoluble Drugs
- High Drug Loading (>75%) Achievable
- Complete Drug Release
- Wide Latitude to Tailor Drug Release
- Release Performance Least Impacted by Hydrodynamic Conditions & pH
- No Fear of Dose Dumping as the Core is Slow-Eroding
- Drug Release at the Target Site With Improved Bioavailability
- Reduced Inter-Subject Variability
- Easy to Swallow
- Strong IP Position
- Technology Available for Commercial Manufacturing
- Proof-of-Concept Demonstrated in Preclinical & Clinical Studies

Features of the BIOROD™ System

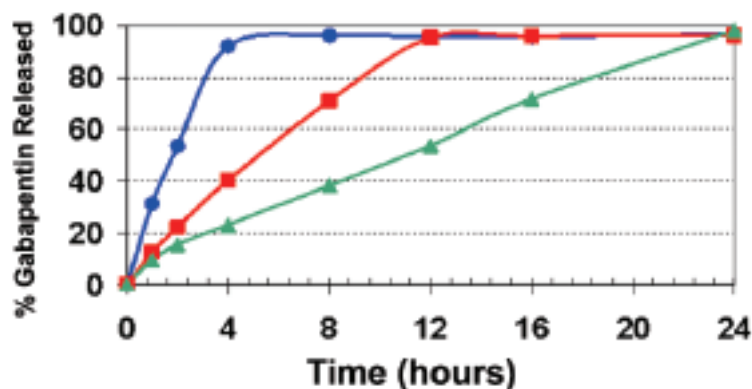
coatings. Drug release can be manipulated by the following:

1. Variation of the formulation and design of the inner drug core;
2. Variation of the rate-controlling polymer(s) and its concentration(s) in the inner drug core;
3. Inclusion of placebo and/or barrier layers within the inner drug core (ie, multilayer tablet design);
4. Variation of the impermeable coating; and
5. Variation of the bioadhesive coating.

The release rate of the drug from the inner core depends on the nature of the drug as well as the ratio between the drug and the rate-controlling polymer(s). By varying the level of rate-controlling polymers, a wide range of controlled-release rates, up to 24 hours, can easily be attained. In addition, the use of multilayer inner cores with eroding placebo and/or barrier layers permits the BIOROD system to provide various drug-release patterns (eg, zero-order, delayed, pulse, ascending, descending). Systems can also accommodate a slow-eroding matrix containing uniformly dispersed rate-controlled beads. Several drug-release profiles achievable with the BIOROD system are schematically depicted in Figure 2. In one example using the design in Figure 2a, gabapentin release profiles of different durations were achieved with the BIOROD system by controlling the level of rate-controlling polymer (Figure 3). In another example, metformin, an anti-hyperglycemic drug with a narrow absorption window, was used in different concentrations in a bilayer inner core (using the design in Figure 2b) to provide a biphasic drug-release profile (rapid drug release followed by zero-order release). Using the design in Figure 2d, the BIOROD system was used to deliver gabapentin in a pulsatile manner (Figure 4). This was achieved through a four-layer inner drug core containing two rapidly disintegrating gabapentin layers, separated by a middle placebo-eroding layer and a bottom non-eroding plug.

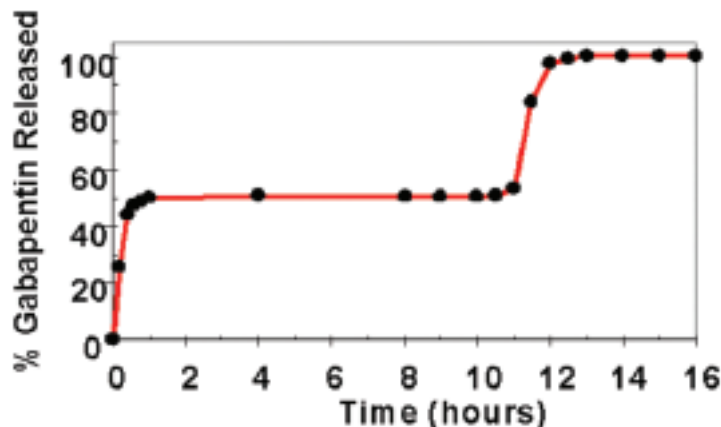
An ascending or descending release profile may be used to optimize the performance of various therapeutic agents. A drug with decreased absorption in the lower GI tract may

FIGURE 3



Different Release Profiles of Gabapentin from the BIOROD™ System

FIGURE 4



Two Pulse Release Profile of Gabapentin from the BIOROD™ System

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GASTROINTESTINAL DELIVERY

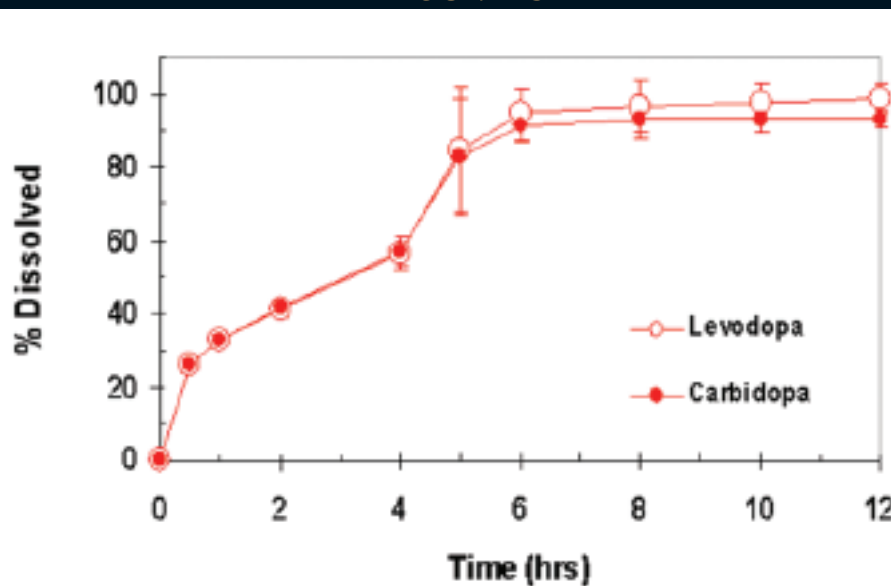
benefit from ascending delivery, thus yielding a more stable plasma profile. In the same manner, if a constant plasma profile is needed, but absorption of the drug is greater in the lower GI tract, a descending release pattern may provide the desired plasma profile.

Levodopa, along with carbidopa, is the most effective drug in the treatment of Parkinson's disease. The GI absorption behavior of orally administered levodopa depends on the GI transit rate because absorption occurs primarily in the proximal small intestine (duodenum/jejunum). In addition, the disease state requires rapid plasma levels in the morning (to provide the "morning kick"), a steady state plasma level during the day, and elevated plasma level in the late day to overcome the "off period," a diurnal pattern observed in studies of patients given a constant-rate levodopa infusion.^{19,20}

Using the design of Figure 2e, the target product profile was achieved using a tri-layer inner core tablet consisting of a top immediate-release drug layer, middle eroding-placebo layer, and bottom controlled-release drug layer (Figure 5). When the immediate-release layer disintegrates, the middle placebo layer and bottom controlled-release layer erode uniformly to provide a zero-order drug release through one end of the BIOROD system. After the middle placebo layer fully erodes, an increased surface area occurs with the controlled-release drug layer and thereby provides the ascending drug release. This gastro-retentive system also resulted in significantly improved levodopa bioavailability and with reduced variability.

The BIOROD system can also accommodate and release two or more drugs in a controlled and customized manner, and is therefore positioned to meet the challenges of combination drug delivery. These combination medications, with two or more existing drugs having complimentary mechanisms of action, offer benefits because of the additive or synergistic nature of the therapeutic effect and the potential for reduced levels of side effects. Compliance with medication treatment regimens and cost savings to patients make combination products a potential life-cycle strategy across key therapeutic areas. Figure 6 shows the release profile of two diabetes drugs, metformin and rosiglitazone, at different release rates from a fixed-dose combination product. This is based

FIGURE 5



Levodopa-Carbidopa BIOROD™ System for Customized Delivery

on the design shown in Figure 2f. A recent study has shown better improvement in glycemic control with this combination due to synergistic effect.²¹

Drug release from the BIOROD system is essentially insensitive to GI motility and food effects. This is mainly because the BIOROD system is a gastro-retentive (ie, bioadhesive), non-disintegrating system in which the inner drug core is protected from the GI environment on all surfaces except the open ends. Therefore, GI motility and transit processes do not have any impact on the integrity of the system or drug release.

MANUFACTURE OF THE BIOROD SYSTEM

The BIOROD system is manufactured using conventional manufacturing techniques and equipment readily available for solid oral dosage forms. Briefly, the drug cores are compressed longitudinally on a multilayer tableting machine (eg, Korsch TRP 900) equipped with deep fill tooling. An inner impermeable coating and outer bioadhesive coating are applied onto the core tablets by pan coating or fluidized-bed coating. The coated cores are then subjected to a laser drilling

process that makes a circular cut in the coatings on each peripheral end. Alternatively, a capsule banding technique can be used to coat only the cylindrical surface of the core. The final coated BIOROD tablets are then applied with a color-coating to impart aesthetics to the final product.

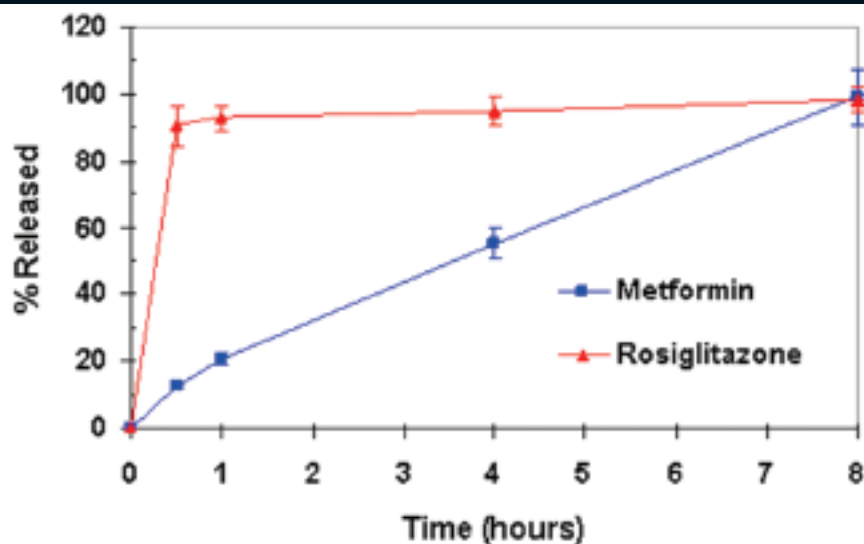
PRECLINICAL & HUMAN STUDIES

Several pharmacokinetic studies have evaluated the delivery of various model drugs with a narrow therapeutic window (eg, levodopa-carbidopa, metformin, gabapentin, oxcarbazepine) via the BIOROD system. These studies demonstrated drug delivery at a constant and consistent rate over an extended duration with significantly reduced inter-subject variability and yielded bioavailability similar or greater than that of the respective immediate-release tablets.

Extensive assessment of localized retention site safety, in addition to chronic and mutagenic safety studies of Spheromer polymers, indicated that the BIOROD system is well tolerated and maintains a strong interaction with the mucosal surfaces. Depending upon the application, the BIOROD system can be fabricated using Spherics' Spheromer polymers or other commonly used hydrophilic bioadhesive polymers.

GASTROINTESTINAL DELIVERY

FIGURE 6



Release Profile of Metformin & Rosiglitazone at Different Rates From the BIOROD™ System

TECHNOLOGY POSITION/COMPETITIVE ADVANTAGE

The BIOROD system offers a number of potential advantages and applications. These are unique to the novel combination of the inner core tablet design and applied bioadhesive polymeric coating, which retains the system at the target absorption site in the GIT (Table 1). The BIOROD is ideally suited to accommodate drugs with narrow absorption windows. This is difficult to achieve even with advanced oral delivery systems that would normally result in reduced bioavailability. By retaining the drug at the target absorption site, a high concentration of drug at the desired site is delivered, while keeping the systemic concentration of drug at a low level. This is particularly useful if the drug causes serious adverse effects if administered systemically in high doses. Due to precise positioning of active(s), placebo, and non-eroding layers/plugs, the system provides flexibility in achieving complex delivery profiles to meet medical needs, including chronotherapy for diseases that are sensitive to circadian rhythms, such as asthma, hypertension, and arthritis. As multiple drugs can be stored inside and released in a programmed manner, the BIOROD system is ideally suited for developing combination products, as a single-unit dose incorporating

different drugs in the same class or different classes of drugs with a common therapeutic effect, thus providing a tremendous opportunity to treat diseases in more effective ways.

SUMMARY

Applications of the BIOROD system continue to be extensively explored at Spherics for developing differentiated products. A number of in vivo studies have been completed in dogs and humans with promising results. The versatility of the system, coupled with its ability to deliver drugs at the target absorption site, will inevitably lead to development of products that can meet specific medical needs.

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BIOGRAPHY



Dr. Avinash Nangia is Senior Vice President of Research & Development for Spherics, Inc., in Mansfield, MA. He has more than 18 years of drug delivery experience, successfully taking numerous drugs from development to market, while holding research management positions at

ALZA Corporation, Glaxo Canada, Inc., and Andrx Pharmaceuticals, Inc. Prior to joining Spherics, he was Director of Research and Development at Andrx, where he was responsible for new technology development and ANDA/ANDA development from preclinical development through Phase IV product support. While at Alza, Dr. Nangia served as Research Fellow and Manager in the Oral Product Development Group. At Glaxo, he was Group Leader for Pharmaceutical Research and Senior Research Scientist for Intramural Basic Research. Dr. Nangia earned his PhD in Pharmaceuticals at the University of Otago, New Zealand, and conducted his Post-Doctoral Fellowship at the University of California, San Francisco. He earned his MS in Pharmaceuticals at the Institute of Technology, BHU, India, and his BS in Pharmacy at the University of Delhi, India. Dr. Nangia holds more than 40 issued/pending patents in the areas of product development and novel drug delivery systems. He is author of more than 45 research papers published in peer-reviewed scientific journals and book chapters and is a member of the AAPS, CRS, American College of Clinical Pharmacology, and American Academy of Neurology.

ELECTRO-OSMOTIC DELIVERY

Proof of Electro-Osmotic Drug Delivery: A Prejudiced Clinical Trial, Delivering From Mouth to Nose

By: Nicholas A. Sceusa, PharmD, and Paul M. Ehrlich, MD

ABSTRACT

We aligned all vectors and mucocilliary clearance contrary to drug delivery, with the exception of the single electrical vector induced by the dosage form. The electrical vector is considerably larger than the other vectors, which made it possible to perform a clinical trial prejudiced against delivery. It would be strong proof-of-concept if delivery were detected in spite of all the opposing vectors, gravity, and mucocilliary clearance. A buffered lozenge containing Zn^{++} was made to induce a lowering of the pH of the mouth with respect to the nose, and thereby a relative reversal of charge between mouth and nose. This reversal established a favorable gradient similar to a concentration cell, in which Zn^{++} could then move over the membrane of the palate into the nose. The experiment was further prejudiced by the fact that the probe did not lie in apposition to the delivering membrane, but was free in the milieu. This form of delivery is suitable for all dual-compartment and mucous membrane anatomical systems and disturbed membrane systems, such as wounds and burns. It can be combined with other novel or classical delivery modalities. In addition, very thin membranes can be breached directly. Restriction of a medication to a given volume, such as an encapsulated tumor, is a unique property of this system.

INTRODUCTION

Previously, we have posed the question of electro-osmotic delivery and presented a mathematical model from first principles in its favor.^{1,2} We now present the results of an IRB-approved, GCP-compliant, controlled

human clinical trial. This trial is submitted as proof-of-concept that electro-osmotic delivery exists and can be induced by the dosage form.

Prejudicing the trial against delivery was achieved by aligning all the delivery vectors, except the electrical vector, contrary to the

FIGURE 1

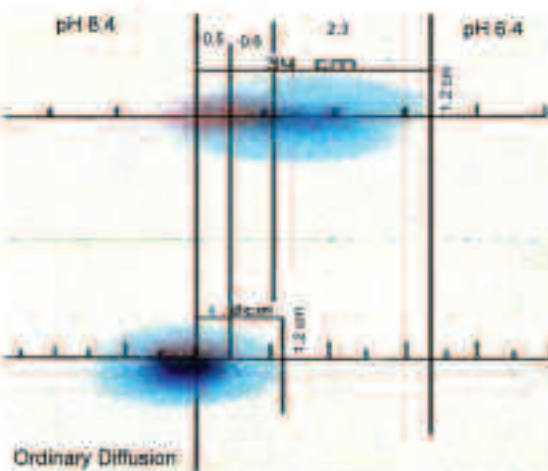
Vector Forces Graphically Analyzed

pH 6.4

pH 8.4

Electro - Osmotic Diffusion

$$J = P[em](C_0 - C_e e^{emF/RT})$$



Ordinary Diffusion

$$J = -P(C_0 - C_i)$$

0.5 cm = 15% ordinary diffusion vector
0.6 cm = 17% advection of water
2.3 cm = 68% electronic component

Reversal of this vector component overcomes the other vectors. This is a unique property of this system. Dyes: FD&C Blue No. 2 and Red 5 & 40. Blue dye has 2-charges; Red dyes are neutral. pH chosen from the physiological range.

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ELECTRO-OSMOTIC DELIVERY

delivery of the Zinc ion trace.

This was done for two reasons. First, the electro-osmotic vector was larger than all the other vectors combined (Figure 1). Second, if detection occurred against all opposition, it was very convincing evidence. This view was fortified by our mathematical model and known physical chemical principles previously discussed. The point was to take into account the generally ignored electro-motive terms of the governing diffusion equation.

Equation 1.

$$J = dQ/dt = -DdC/dx = Pf(EmF)[C_0 - C_1 e^{(EmF/RT)}]$$

Where P = permeability coefficient of the medium = -D/dx; D = diffusion coefficient, which is temperature dependent; f means *function of* and is part of mathematical notation; Em = -2.303kT Log Keq (Boltzmann Expression for Emf); Em_{37°} = -61.5 x 10⁻³ volts x Log

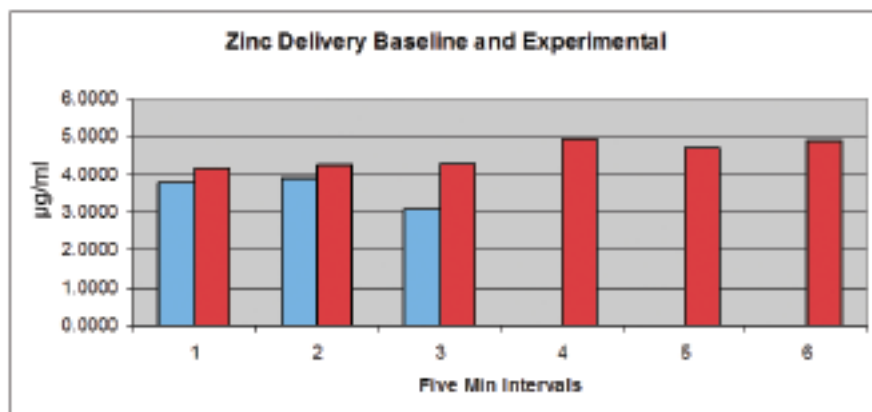
TABLE 1

	Data		
	1.9376	-	2.4520
	4.5950	-	4.7020
	3.3120	3.8300	3.4440
	4.3490	5.2210	
	1.0530	0.7780	0.9600
	1.7310	1.7960	3.2750
	1.6960	1.4700	1.5810
	6.3460	5.0610	3.4140
	5.9610	6.1170	4.0250
	4.9380	2.8240	2.0760
	4.2650	5.0820	3.9670
	3.6110	4.3320	2.8680
	4.6660	6.2450	5.3860
	2.9880	4.9230	2.3080
	5.6920	3.0500	2.4040
Total	57.1406	50.7290	42.8620
N	15.0000	13.0000	14.0000
Average	3.8094	3.9022	3.0616
Grand Average	3.5911		

*Blank spaces indicates lost data

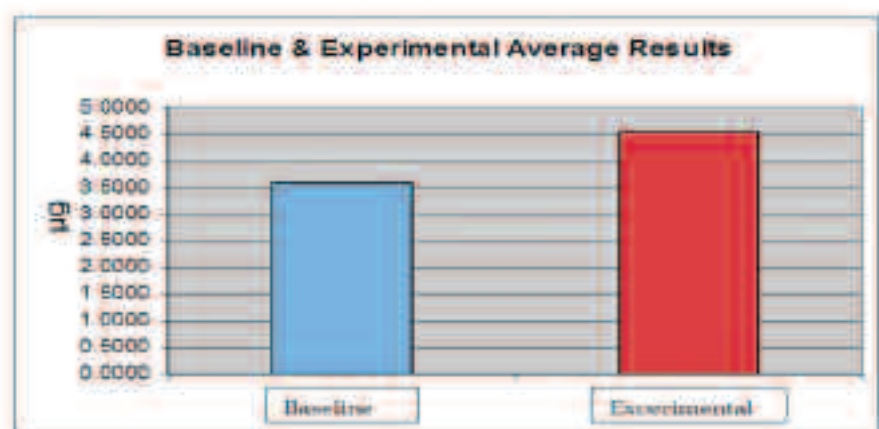
Baseline Mucous Results µg/ml Zinc

FIGURE 2



Baseline & Experimental Results Compared

FIGURE 3



F-Test Two-Sample for Variances

	Baseline	Experimental
Mean	3.58884851	4.532616279
Variance	2.48114923	4.494796051
Observations	42	86
df	41	85
F	0.55200485	
P(F<=f) one-tail	0.01860757	
F Critical one-tail	0.62711969	

BASELINE & EXPERIMENTAL AVERAGE NASAL ZINC ION RESULTS (µg/ml)

The averaged baseline and averaged experimental values were significant. F-Calculated was less than F-Critical one tail.



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ELECTRO-OSMOTIC DELIVERY

K_{eq}/Z ; R = universal gas constant and T = temperature in degrees Kelvin; $K_{eq} = [\text{products}]/[\text{reactants}] = [\text{oxidized}]/[\text{reduced}] = [pH1]/[pH2]$; and Lewis definition: oxidized = loss of electron etc. All positive or negative charges are equal.

We then obtain by the aforementioned substitutions the unidirectional flux equation:

Equation 2.

$$J = dQ/dt = \frac{-2.6 D \text{ Log}([pH1]/[pH2])[C_0 - C_i e^{(-2.6 D \text{ Log}([pH1]/[pH2])}] }{dx}$$

Here, the flux J is now made proportional to pH and is a function of EmF or electromotive force.

MATERIALS & METHODS

The experiment was statistically designed using 15 subjects, emulating the local population of normal male and

female subjects between the ages of 18 and 60. The statistical number needed was 13 subjects, and thus there was sufficient power. The trial was conducted in an open fashion without blinding because the values obtained were machine generated and analyzed by outside independent laboratories.

FDA approved for human use probes and fraction collecting equipment were made by CMA-Microdialysis of Chelmsford, Massachusetts. The probe was a CMA 70 catheter, 100-mm flexible shaft, with a 10-mm membrane. The analytical work was done and certified by Dr. Jan Kehr of the Karolinska Institute, Stockholm, Sweden. Blood plasma samples were taken in the usual manner.

Zinc ion (Zn^{++}) was used as the trace. The dosage form was a homeopathically compounded lozenge, or oral tablet, entirely made from food ingredients found in the Generally Regarded as Safe (GRAS) list.³ All of the lozenge's ingredients were governed exclusively by the Dietary Supplement Health and Education Act of 1994 and the Homeopathic Pharmacopœia of the United States (HPUS).^{4,5}

The protocol was conducted in compliance with GCP and all applicable requirements of federal, state, and local authorities. There was no infringement of any proprietary or patented product.⁶

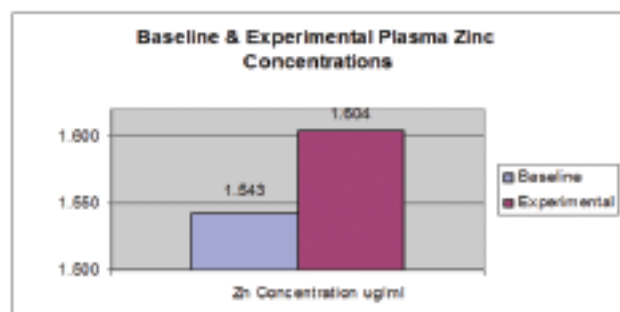
The lozenge was designed to buffer the pH of the mouth at approximately pH 5.4. Our patients' noses had an average nasal pH of 6.35. The electrical potential between compartments as measured by the method of Selimoglu et al using nitrazine pH paper was consistently at $\Delta = 0.95$ pH units in favor of transport to the nose from the mouth.⁷ The slight change in expected pH value may have been due to the production of bicarbonate by the sublingual glands.

Inducing the pH change takes control of the corresponding electrical vector, allowing us to manipulate the directions of ionic flow and transport. Because the electrical vector is many times more powerful than the other vectors acting, we may stop or reverse the ionic flow for the time the induced field is present.

The natural electrical gradient lies in the same direction as gravity and the mucociliary clearance and aids the nose to clean itself. The reversed gradient allows drug delivery to occur over the palate and into the nose from the mouth.

In order to measure delivery, an in situ microdialysis probe was placed in the nostril and introduced past the turbinates to the level of the eustachian tube to freely sample the milieu. The junction of the eustachian tube with the naso-pharynx near the end of the third turbinate was used as a physiological marker for the probe, allowing consistent placement. The probe, which was

FIGURE 4



F-Test Two-Sample for Variances

	Baseline	Experimental
Mean	1.54372	1.604258157
Variance	0.41817	0.167912146
Observations	49	84
df	48	83
F	2.49038	
P(F<=f) one-tail	0.00013	
F Critical one-tail	1.50885	

BASELINE & EXPERIMENTAL PLASMA ZINC CONCENTRATIONS

A difference of 0.061 between the baseline and experimental plasma values was not significant. The calculated F is larger than F critical one tail.

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ELECTRO-OSMOTIC DELIVERY

not in apposition to the membrane, induced the production of mucous, which leads us to suspect that the delivery may be higher than actually measured because of the extra production of mucous the probe induced.

At 5-minute intervals, 20-microliter dialysis samples were taken from each subject: three controls of deionized water, three from the nasal mucous for baseline, and six from the nasal mucous with the lozenge in place. Simultaneous blood plasma samples were taken at baseline and experimental intervals. The control samples were taken to determine the level of zinc in the lines and probes due to manufacturing.

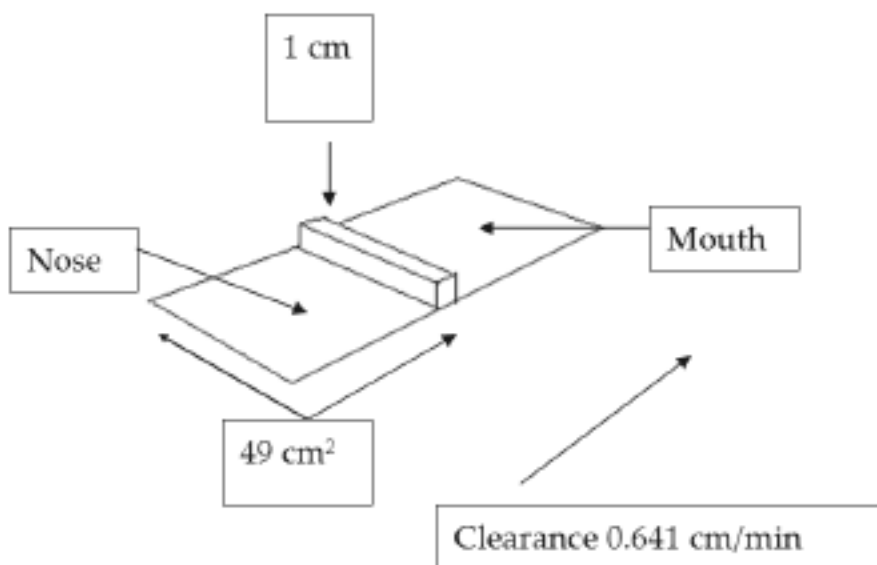
RESULTS

There was less than 2.60 $\mu\text{g/ml}$ of zinc in the line and probes. The baseline nasal zinc was 3.59 $\mu\text{g/ml}$, and 4.54 $\mu\text{g/ml}$ in the experimental. The differences between experimental and baseline (0.95 $\mu\text{g/ml}$) were the same with or without subtraction of the controls. The subtraction of the controls from the baseline and experimental values did not affect the results. The unsubtracted results are presented in Figures 2 & 3 and Tables 1 & 2. The difference between Baseline and Experimental was 0.95 $\mu\text{g/ml}$, and this was significant by F-Test ($p = 0.019$). The difference in the two plasma zinc concentrations was 0.061 $\mu\text{g/ml}$ and was not statistically significant by F-test. It is presented in Table 3 and Figure 4.

DISCUSSION

The nasal mucous samples showed a statistically significant difference between baseline and experimental values, while the plasma samples did not. This result demonstrates that systemic

FIGURE 5



Sheet Model of the Naso Pharynx

TABLE 2

	2.9420	3.0980	2.5800	-	2.5300	3.3650
	5.4890	5.7870	5.8580	5.8160	5.9040	8.2800
	3.0870	3.0440	5.8330	5.5060	-	-
	3.9950	4.6460	3.0910	4.5920	5.0460	4.6230
	0.9580	2.0860	1.6820	1.8350	1.9020	2.1450
	2.0220	1.6350	2.1550	3.5720	4.1960	3.0890
	2.4100	2.7150	2.4020	2.6160	2.6910	2.7230
	4.5760	4.4900	4.4100	5.4700	4.3960	5.1840
	2.7070	5.6590	5.5930	5.1170	5.7150	5.8170
	3.4350	4.3380	7.1760	5.6510	3.4940	3.4740
	5.2820	2.2010	4.9880	4.9380	4.8970	4.1160
		3.7280	4.3300	5.4710	5.2140	5.9680
	4.4950	5.7490	1.9870	6.7090	3.9830	4.3250
	6.8750	3.2390	3.5580	2.7490	4.3100	6.3430
	10.4680	11.1150	8.4570	9.1710	11.3870	9.1040
Total	58.7410	63.5300	64.1000	69.2130	65.6650	68.5560
N	14.0000	15.0000	15.0000	14.0000	14.0000	14.0000
Average	4.1958	4.2353	4.2733	4.9438	4.6904	4.8969

* Blank spaces indicate lost data

Experimental Nasal Mucous Results $\mu\text{g/ml}$ Zinc



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TABLE 3

Baseline	Baseline	Experimental	Experimental
1.275	1.001	1.426	1.367
1.249	1.066	1.184	1.609
1.145	1.648	1.302	1.642
2.643	1.354	1.446	1.557
1.766	1.426	1.171	1.249
1.779	1.328	1.275	1.374
1.603	1.374	1.851	1.367
1.452	Average 1.543	2.113	1.609
1.158		1.524	1.642
1.773		2.734	1.557
1.400		2.937	1.243
1.485		1.746	1.452
2.394		1.439	1.622
1.243		1.622	1.426
1.341		1.347	1.498
1.491		1.452	1.831
1.302		1.792	2.714
2.407		1.537	1.962
1.361		1.485	1.374
1.491		1.001	1.164
1.498		1.164	1.701
1.596		1.354	1.459
1.374		2.080	1.380
1.328		1.321	1.472
1.432		1.583	1.308
1.570		2.021	1.511
1.426		1.406	1.616
1.524		1.347	1.334
1.217		2.093	2.165
1.426		1.295	1.073
1.524		1.504	1.387
1.217		1.845	1.517
1.341		1.426	1.413
1.190		1.544	1.642
1.544		1.648	1.544
1.596		1.171	3.663
1.308		1.786	1.642
1.491		1.877	1.661
1.328		1.962	1.511
1.616		1.786	1.596
5.409		1.936	1.603
1.033		1.249	1.740
1.223		1.374	Average 1.604

Plasma Baseline & Experimental Values $\mu\text{g/ml}$ Zinc

delivery of zinc can be ruled out, and delivery of zinc must occur from the mouth to the nose. How much is delivered and what are the characteristics of the delivery? We may be able to answer these questions by using the geometric model developed in our previous work. The placement of the probe was at the end of the third turbinate near the eustachian tube junction with the pharynx. This anatomical placement corresponds to a uniform position just anterior to the midpoint of our flat sheet model. We estimate that the probe was about 1 cm above the surface of the membrane by direct observation. By estimating the volume of liquid in this domain and multiplying by the concentration, we can estimate the amount of zinc delivered by using the approximate velocity of the mucocilliary clearance.

Referring to our model, the length and width of the path is 7 x 7 cm, with an estimated height of 1 cm. Thus, the nasal half of the sheet holds 49 cc of fluid. This fluid is considered to result from all sources and includes flow from the turbinates and sinuses as well as probe-induced mucous. The average mucocilliary clearance (Table 4) is considered to be 0.641 cm/minute. To travel a distance of 7 cm clearing the nasal half of the sheet and its volume of 49 cc of fluid requires 10.92 minutes.

Because the lozenge dissolves over 30 minutes, mucocilliary clearance clears this 49-cc volume of mucous 2.75 times. This becomes 134.75 cc of fluid cleared over 30 minutes. The approximate steady state concentration detected by probe is nearly 1 $\mu\text{g/ml}$ of zinc. This translates into approximately 0.135 mg of zinc ion delivered (Figure 5). This calculation does not take into account the other turbinates, sinuses, or the mucous induction due to the probe, but assumes them to be contributory to the milieu. Thus, delivery

ELECTRO-OSMOTIC DELIVERY

TABLE 4

Source	Range	Average Speed
Ann Otol Rhinol Laryngol. 2002;111(1):779	2.9 to 5.66 mm/min	4.28 mm/min
Rhinol. 1986;24(4):241-247	3.3 to 8.2 mm/min	5.3 mm/min
Arch Otolaryngol. 1982;108(2):99-101	5.8 to 13.5 mm/min	9.65 mm/min
Grand Average Velocity		6.41 mm/min

Mucocilliary Transport Velocity

may be greater than is estimated here.

Calculation Summary

- $7 \times 7 \text{ cm} \times 1 \text{ cm} = 49 \text{ cc fluid}$
- $7 \text{ cm} / 0.641 \text{ cm/min} = 10.92$ minutes to clear nasal end of sheet once
- 30 min lozenge dissolution time / 10.92 minutes per clearance = 2.75/clearances per 30 minutes
- $49 \text{ cc fluid} \times 2.75 = \text{Volume cleared in 30 minutes} = 134.6 \text{ cc}$
- $134.6 \text{ cc} \times 1 \mu\text{g/cc detected} = 134.6 \mu\text{g Zn}^{++} = 0.1346 \text{ mg Zn}^{++}$ delivered

This amount of drug is well within the range of the minimal effective concentration of most drugs, when directly delivered, and corresponds to delivery at nearly 1 pH unit difference. This increases exponentially by increasing the difference between compartments (pH), according to Equation 2.

CONCLUSION

Electro-osmotic delivery exists and is potentially a very useful modality in drug delivery. Since the governing flux equation is responsive to the ratio of the pHs in an exponential manner, a small difference in this ratio makes a large difference in delivery. By reversing this

ratio, a charged medication can be forced to remain in one place, within a solid tumor, for example. This can sensitize the tumor to radiation and chemotherapy, resulting in a reduction of these agents, and localization of therapy. This modality predicts new forms and new activity for old forms. Particularly, extremely thin skin patches, lozenges, bandages, and wound staunching pastes are foreseen.

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BIOGRAPHIES



Dr. Nicholas A. Sceusa was born and privately educated in New York City. He graduated from Syracuse University with a BS in Biology and a minor in Chemistry. During the learning phase of his career, he studied at the Sorbonne in Paris and the University of Clermont-Ferrand in France. Familiar with European

methods of administrations and scientific development, he paid particular attention to the medical sciences and the development of the national cultures of Spain, Italy, and France. Dr. Sceusa earned his BS in Pharmacy at the Arnold and Marie Schwartz School of Pharmacy and Allied Health Sciences. He practiced pharmacy for several years before joining the drug development team of Revlon Health Care Group, Inc. His research interests were furthered by courses at New York University in Physical, Organic, and Inorganic Chemistry and Statistics. Dr. Sceusa earned his PharmD from the University of Illinois at Chicago, specializing in the scientific and drug development aspects of the field. He is experienced in Clinical Trials Project Management & Monitoring, Clinical Trials Coordination and Drug Information, various aspects of Informatics and Safety Evaluation, and has practical experience in Drug Safety, Adverse Events Reporting, and Regulatory Affairs. Medical research interests include cardiovascular disease (particularly hypertension), infectious and pulmonary disease, viral attachments sites, adhesion molecules, allergy, endocrinology, and obesity. He holds patents in biofiltration and on the unique Teorell-Meyer Dosage Forms.



Dr. Paul M. Ehrlich was born and privately educated in the New York Metropolitan Area. He prepped at the prestigious Taft School in Watertown, CT. He is an alumnus of Columbia University and a graduate of New York University Medical School. His post-doctoral education was extensive. From 1977, he has maintained a

private practice in Allergy and Immunology and has been regarded as one of New York's Best Doctors since this publication was first published. Dr. Ehrlich completed his pediatric clerkship at the Hospital for Sick Children, in London, UK, was a member of the Department of Allergy and Immunology at the Walter Reed Army Hospital in Washington, DC, and served as a Lt. Commander in the United States Navy during the Vietnam era. He is a Diplomate of the National Board of Medical Examiners, the American Board of Pediatrics, and the American Board of Allergy and Immunology. Dr. Ehrlich is a Fellow of the American Academy of Pediatrics, The American Academy of Allergy, Asthma and Immunology, The American Thoracic Society, and takes an active part in many professional societies too numerous to mention. To add to the list of his accomplishments, Dr. Ehrlich is the Medical Editor of the MA Report and a member of the Editorial Advisory Board of *Asthma Management*. He is the author of *What Your Doctor May Not Tell You About Your Children's Allergies or Asthma*. He is presently Clinical Assistant Professor of Medicine in the Department of Pediatrics at NYU Medical Center in Manhattan.

PULMONARY DELIVERY

Pulmonary Drug Delivery: Technology, Regulation & Testing

By: Mark Copley, MEng (Hons)

INTRODUCTION

The market for inhaled pharmaceuticals is growing fast. Rising levels of pulmonary disease, rapid expansion in generics, and recognition of the intrinsic benefits of the pulmonary route for systemic delivery, are all fuelling demand. Recent setbacks in the development of inhaled insulin have highlighted the technical and commercial complexities of the marketplace, but the trend toward pulmonary drug delivery looks set to continue; development activity remains intense and competitive.

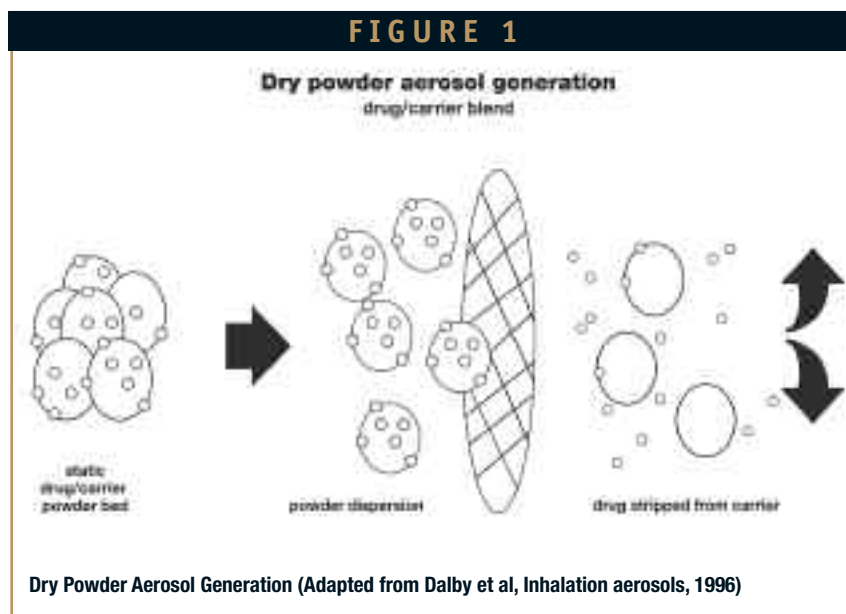
The following reviews current inhalation technology, the associated regulatory framework, and the test methods specified by the regulatory bodies for approval: delivered dose uniformity and aerodynamic particle size measurement.

DEVICES FOR INHALED DRUG DELIVERY

Devices used for inhaled drug delivery are collectively referred to as orally inhaled and nasal drug products (OINDPs). The range is broad, encompassing nebulizers, nasal sprays, and inhalers (metered dose, dry powder, and aqueous droplet). Hybrid designs, combining the advantages of different devices, are also becoming increasingly common.

Metered Dose Inhalers (MDIs)

MDIs, or pMDIs (pressurized metered dose inhalers), remain the most widely used, particularly for treating chronic obstructive pulmonary disease (COPD) and asthma. MDIs use a propellant to consistently deliver a fixed volume of a liquid formulation (solution or suspension) in spray form. They are small,



inexpensive, convenient for the user, and suitable for a wide range of drugs.

Formulation development for MDIs can, however, be challenging, an issue brought into focus by the banning of chlorofluorocarbons (CFCs); the shift to new hydrofluoroalkane (HFA)-based propellants has necessitated much reformulation. MDIs require the user to have good coordination and technique, and the actuation force needed means they are not always suitable for elderly or paediatric users. Improved spacers (or holding chambers) and new breath-actuated MDIs are helping to overcome these problems.

Dry Powder Inhalers (DPIs)

In an industry that already produces many powder formulations, DPIs are an attractive option. Forecasts suggest that they will account for up to 50% of the global inhaler market by 2012.¹ Typically, the active pharmaceutical ingredient (API) is carried on an excipient but is stripped from the carrier during dispersion/aerosolization (Figure 1). API

enters the lung; the carrier is ingested.

DPIs are well suited to systemic drug delivery and are perceived as more environmentally friendly than MDIs. Breath-actuated, they synchronize drug delivery with inhalation. However, their relatively higher cost and reliance on inhalation strength and duration are potential drawbacks.

Aqueous Droplet Inhalers

Aqueous droplet inhalers are a new generation of devices that deliver a pre-metered dose of liquid formulation, without using a propellant. They actively aerosolize the liquid, producing a cloud of fine particles for accurate, gentle, patient-independent dosing. Aerosol generation method varies from device-to-device.

These inhalers generally deliver a higher fine particle fraction than DPIs or MDIs, enhancing API delivery to the lung. They are easy to use and are associated with low-dose variability but, as with any multi-dose liquid systems, microbial contamination can be a problem. High

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PULMONARY DELIVERY

production costs associated with their complexity are also a drawback.

Nebulizers

Like aqueous droplet inhalers, nebulizers actively aerosolize a liquid formulation. Nebulizers, however, operate continuously once loaded. The inhaled dose is a function of usage time and user breathing profile and is not generally pre-metered.

Nebulizers are widely used at home and in hospitals, and demand little or no coordination for effective use. The prescribing clinician specifies the drug/nebulizer combination. As a result, nebulizers have been classified by the regulatory authorities as medical devices rather than pharmaceutical products. Issues with nebulizers include cost, efficiency, inter-brand variability, and convenience. Conventional nebulizers tend to be large and heavy and require either a compressed air or electricity supply. New mesh technology is an improvement, delivering portable, silent, battery-operated devices.

Nasal Sprays

Historically used to deliver locally acting drugs, nasal sprays are now of interest for systemic drug delivery. Tissues behind the nose offer a large surface area for rapid drug absorption, while the olfactory region at the top of the nasal cavity provides nose-to-brain entry for drugs acting on the central nervous system.

Like inhalers, nasal sprays can be liquid- or powder-based. Aqueous systems can be manually actuated or propellant driven. They are commonly multi-dose, although unit-dose devices are popular for delivering vaccines and pain relief. Powder-based systems are particularly suitable for high-concentration delivery and for materials such as peptides, antigens, and hormones.

REGULATORY ORGANIZATIONS & THEIR ROLES

Currently, there are no worldwide regulatory standards for OINDPs. In Europe, responsibility for their regulation lies with the European Medicines Agency (EMA); in the

US, it is the Food and Drugs Administration (FDA). The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is working toward harmonization.

New guidance issued in October 2006 by EMA, in conjunction with Health Canada (the regulatory body for Canada), covers all OINDPs, including nebulizers and nasal sprays, harmonizing testing for all devices.² Nebulizers were previously tested according to the European Committee for Standardization (CEN) Standard for Respiratory Therapy Equipment, EN 13544-1. In the US, regulation for OINDPs is detailed in a range of documents issued by the FDA.³⁻⁷

On a practical level, the safety and efficacy of drugs is ensured through adherence to the quality standards, requirements, and tests detailed in the pharmacopoeias.^{8,9} Drug delivery devices are also governed by the standards laid down by the International Standards Organization (ISO). Documents relating to aerosol drug delivery devices and nebulizing systems are currently in development.^{10,11}

PRODUCT TESTING

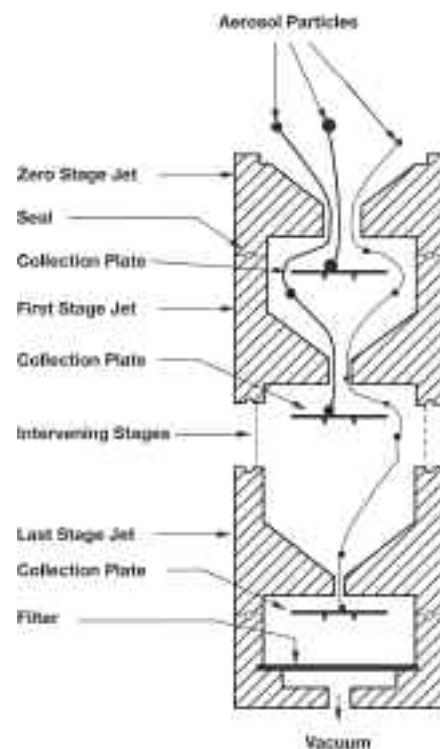
OINDP performance is characterized principally by measuring delivered dose uniformity and aerodynamic particle size. Dose uniformity testing confirms consistent delivery of the specified amount of drug. Aerodynamic particle size measurement broadly indicates where in the respiratory system the drug will be deposited, but primarily exists to ensure consistency of aerosol generation. For drug delivery to the lungs, it is generally accepted that particles should lie in the size range 1 to 5 microns. This portion of the dose is referred to as the fine particle fraction (FPF).

DELIVERED DOSE UNIFORMITY

Methodology

Delivered dose is measured by firing the test device into a sampling apparatus

FIGURE 2



Schematic of a Cascade Impactor (USP 31)

containing a filter. The dose is captured then recovered for chemical or gravimetric quantification: % API and sometimes overall weight. Air is drawn through the sampling apparatus during testing to simulate inhalation. MDIs are relatively insensitive to flow rate because the aerosolization and dispersion mechanism is generated by the force of the propellant. Therefore, for MDIs, air flow-rate is set at an arbitrary 28.3 L/min (1 scfm), but for DPIs, the test regime is more complex.

DPI aerosolization performance depends on inhalation strength and duration. Because adult inhalation results in a pressure around 4 kPa less than atmosphere at the mouth, air flow rate is set to generate a 4 kPa pressure drop across the DPI during testing. With a low-resistance device, this air flow may be very high, so an upper limit of 100 L/min is specified. Test duration is set on the basis of the total air volume typically inhaled in one adult breath; the pharmacopoeias recommend 4 L, and the FDA recommends 2 L. Additionally,

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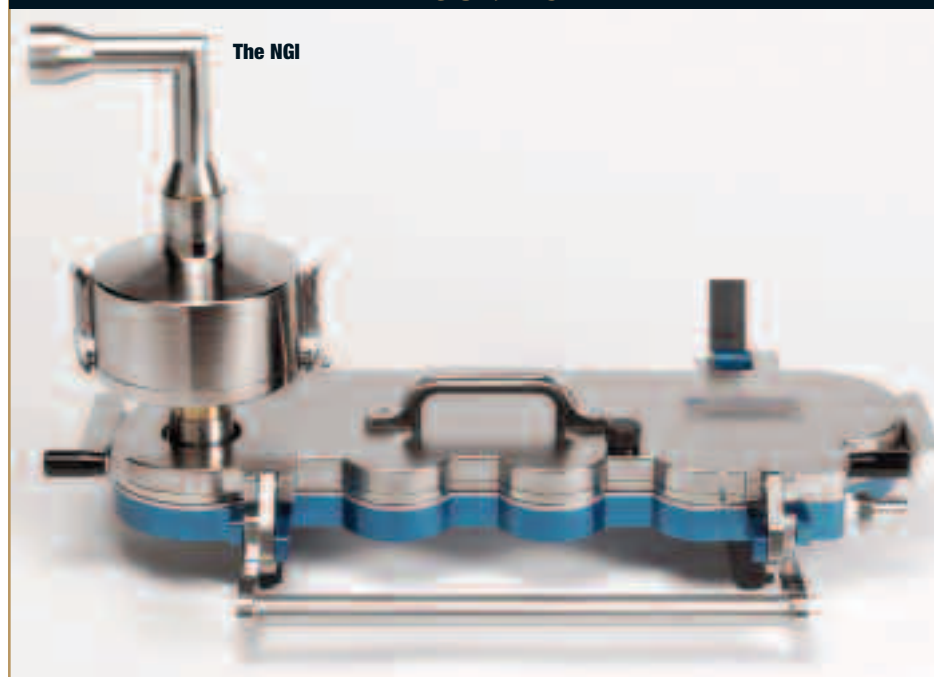
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FIGURE 3



a range of flow rates and total air volumes may be considered to ensure drug delivery consistency under non-ideal conditions or unintentional misuse.¹²

Instrumentation exists to simplify the set-up of DPI testing. For instance, the TPK 2000 critical flow controller (Copley Scientific, UK) drives the set-up process, records all required test parameters, and provides the steady air flow rate necessary for analysis.

Nebulizer testing is also somewhat complex because the amount of drug delivered is a function of the users' breathing patterns and length of use. New test methods proposed by the pharmacopoeias recognize this and specify using breath simulators for delivered dose assessment.^{13,14}

These methods define standardized flow conditions for delivered dose testing to reflect an adult breathing pattern: 500 mL tidal volume; sinusoidal waveform; 15 cycles per minute; 1-to-1 inhalation/exhalation ratio. Conditions may be varied to reflect, for example, paediatric use. Active substance delivery rate and the total active substance delivered are determined.

Assessing Results

The regulators and pharmacopoeias define criteria for test success, specifying the number of units to be tested and acceptable deviation from the label claim. FDA, EMEA, US Pharmacopoeia (USP), and European Pharmacopoeia (Ph Eur) terminology all differ slightly, making it essential to refer to the relevant documentation when developing test procedures.

For multi-dose units, dose uniformity must be ensured throughout the life of the inhaler. The USP and Ph Eur recommend for a multi-dose MDI or DPI with a labelled number of doses, assaying the first three, middle four, and final three doses. FDA guidance also specifies how many devices to test. Doses not assayed are fired to waste.

AERODYNAMIC PARTICLE SIZE MEASUREMENT

Aerodynamic particle size is measured using a multi-stage cascade impactor, a precision-engineered instrument that divides a sample into size fractions on the basis of

particle inertia. Uniquely, this allows collection of the entire dose and chemical assessment of API content as a function of aerodynamic particle size. Drug is typically rinsed from the impactor using organic solvents/buffer solutions and quantified by high-pressure liquid chromatography (HPLC). Figure 2 illustrates the basic principles of cascade impactor operation.¹⁵

The pharmacopoeias recommend several different commercially available impactors for routine testing. These include the Next Generation Impactor (NGI) (Figure 3) and Andersen Cascade Impactor (ACI) (Figure 4), which are used globally for the majority of OINDP analysis, as well as the Multi-Stage Liquid Impinger (MSLI) still widely used in Europe. Despite their limitations, single-stage impingers are also employed, albeit increasingly rarely, for rapid screening during early product development and for some QC applications.

Aspects of Testing

Cascade impaction is a complex analytical technique, and many factors affect performance. Air flow rate through the instrument is particularly important because it determines velocity through the nozzles. This directly influences particle inertia and the aerodynamic diameter of particles captured on each stage (stage cut-off diameter). It is therefore essential to set and control air flow rate and understand its impact on stage cut-off diameter.

For MDIs and DPIs, the flow rates for aerodynamic particle size measurement are as specified for dose uniformity testing: 28.3 L/min (or 30 L/min) for MDIs, and anything up to 100 L/min for DPIs. Nasal sprays are also tested at 28.3 L/min in most cases. Nebulizers are tested at a flow rate of 15 L/min (no sinusoidal pattern), broadly representative of adult tidal flow rate.

Air is drawn through a cascade impactor using a vacuum pump, with a control valve setting flow rate (Figure 5). In the case of DPIs, sonic (or critical) flow through this valve maintains steady flow through the inhaler in the event of fluctuations caused by the pump, or subtleties when switching between device and flow meter. To achieve sonic flow, P3 must

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be less-than or equal-to half P2. This is verified during set-up, before actuating the device.

If flow rate is accurately known then the question that remains is: what are the stage cut-off diameters under these conditions? The ACI was originally designed to operate at 28.3 L/min; additional stages allow modified configurations for operation around 60 and 90 L/min. Calibration data exist for the modified version of the impactor, and stage cut-off diameters can be calculated, based on impactor theory, for all flow rates across this range. As flow rate moves away from the calibration points, the theoretical equations become increasingly inaccurate. Furthermore, stage overlap increases with increasing flow rate, so the instrument discriminates less clearly between successive fractions.^{16,17}

To overcome these and other issues, the NGI was developed based on the requirements of 16 major pharmaceutical companies involved in the development of inhaled products. The NGI has well-calibrated performance, following rigorous calibration of an archival NGI at 30 to 100 L/min and then, in a separate exercise, at 15 L/min. Equations are available to calculate stage cut-off diameters for any flow rate within this overall range.^{18,19} Any properly maintained NGI manufactured to the design specification will deliver this aerodynamic performance.

Other critical aspects of cascade impactor testing include:

PARTICLE RE-ENTRAINMENT – particles rebounding from a collection surface will be re-entrained in the air stream, ultimately collecting on the wrong stage further downstream. Validated coating of the surface with glycerol or silicone, for example, normally deposited from a volatile solvent, minimizes this effect, which is mostly encountered with DPIs.

NUMBER OF DOSES PER TEST – dose number should be kept to the minimum while ensuring sufficient material for a reliable assay of API.

MAINTENANCE – daily checks for corrosion, wear, and tear – damaged seals, nozzles, and collection surfaces.

FIGURE 4

Andersen Cascade Impactors



MENSURATION – is good practice, and regular stage mensuration is essential. This involves measuring all the critical mechanical dimensions of the impactor and can be carried out by the original supplier. It establishes whether the impactor's performance remains within the range defined by the manufacturing specification of the instrument and those specified in USP and Ph Eur.²⁰

LEAK TESTING – is an important aspect of ensuring impactor integrity. Air leakage into the impactor will not directly affect mass balance, but could influence the air flow through the instrument, and that measured at the inlet, with consequences for determining aerodynamic particle size distribution (APSD).

ELECTROSTATICS – as build-up of electrical charge can impact particle behavior, grounding the impactor is a sensible precaution. Ionizers may also be used to neutralize electrostatic charge accumulation in the testing environment.

ENVIRONMENTAL CONDITIONS – monitoring temperature and humidity is important. With hygroscopic formulations, direct control of environmental conditions may

be essential in order to reduce potential variability. Further details are available regarding best practice for cascade impaction testing.²¹

Assessing Results

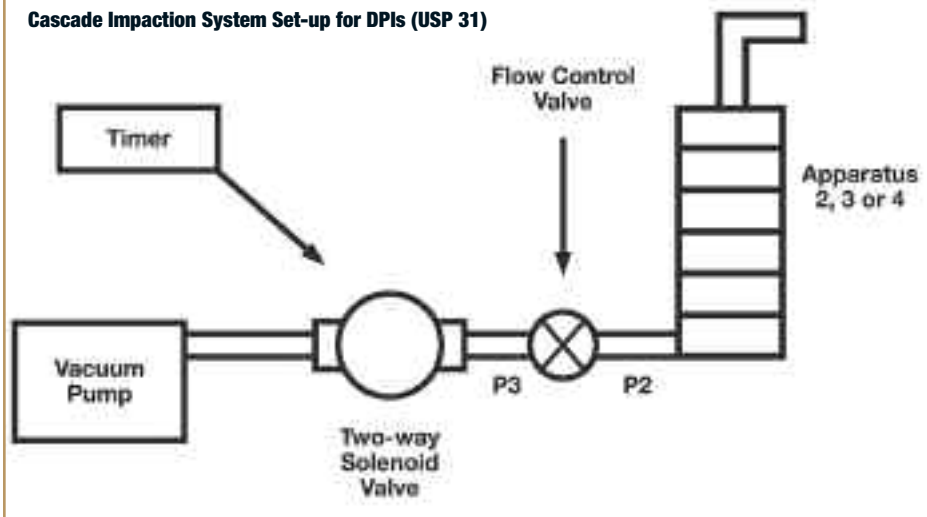
Ideally, the entire dose delivered to a cascade impactor should be captured in/on: the induction port, pre-separator (if used), collection surfaces, final filter, or Micro-Orifice Collector (MOC). Sample is recovered from all these internal surfaces after each analysis. In reality, impactor inter-stage losses occur, and their minimization was one of the design specifications for the NGI, which meets the USP target value of < 5%, avoiding the need for drug recovery from inter-stage passageways and nozzles between consecutive runs, in most cases.

The regulators and pharmacopoeias specify acceptable ranges for impactor mass balance relative to the mean (or target) delivered dose performance of the device. Failure to meet these requirements normally requires re-testing. Drug mass-per-stage data is then often analyzed and reduced to the following key parameters for characterizing the delivered dose:

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FIGURE 5

Cascade Impaction System Set-up for DPIs (USP 31)



- Fine Particle Dose (FPD) – drug less than the fine particle dose specification (typically < 5 microns, or the impactor stage with a cut-off diameter closest to this value)
- Fine Particle Fraction (FPF) – FPD expressed as a percentage of the delivered dose
- Geometric Standard Deviation (GSD)
- Mass Median Aerodynamic Diameter (MMAD)

Full characterization of the dose is still normally required, although the use of stage or particle-size groupings, relating to the critical aspects of the distribution, may be accommodated.

SUMMARY

Inhaler technologies are developing rapidly as the pharmaceutical industry moves to exploit the benefits of pulmonary drug delivery. In response, regulatory bodies, the pharmacopoeias, and expert groups have all invested heavily in developing appropriate test methods. The new inhaled products guidance from the EMEA, the draft pharmacopeia

monographs, and the soon-to-be-completed ISO standards for devices, all reflect the ongoing nature of this work.

Delivered dose uniformity and aerodynamic particle size are key parameters for all OINDPs. Continuing harmonization of standards will simplify testing and reduce workload in this area. Test methods have developed significantly in recent decades in line with the evolution of commercially available equipment. Specialists, such as Copley Scientific, now provide a wide range of instruments and accessories that simplify and accelerate data acquisition. Rapid information gathering will be vital in the future, with further modifications to cascade impactors possible, as the industry implements Quality by Design to reduce risk and enhance process efficiency.

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BIOGRAPHY



Mark Copley graduated from the University of Bath in 2000 with a Masters in Aerospace Engineering. For the past 8 years, he has been sales manager and product

specialist for Copley Scientific's range of inhaler testing equipment and is considered to be a leading authority in testing methods and systems for metered-dose inhalers, dry powder inhalers, nebulizers, and nasal sprays. Mr. Copley also provides application support and consultancy, and runs focused training courses and workshops for the inhaled drug testing sector of the pharmaceutical industry. He is an invited member of the European Pharmaceutical Aerosol Group (EPAG) impactor sub-team and has made contributions to the Inhalanda working group, leading to subsequent revisions to Ph Eur and USP monographs.

SENSORY-DIRECTED FORMULATIONS

Taste Optimization of a Model Oral Spray Drug Product

By: Jeffrey H. Worthington, MBA; David A. Tisi, MS; Frank E. Blondino, PhD; and Foyeke O. Opawale, PhD

INTRODUCTION

Technology advances are leading to the development of novel oral dosage forms that may provide faster onset of action, fewer side effects, and improved patient dosing (convenience). One such technology is oral sprays. NovaDel Pharma Inc. utilizes oral spray systems to deliver a broad range of APIs to the systemic circulation through the highly perfused lining of the oral cavity. NovaDel's core technology offers substantial benefits compared to other modalities of drug administration, including faster onset of action, increased drug bioavailability due to avoidance of first-pass effect in the liver, avoiding the need to take medication with water, and avoiding the need to swallow. Drug delivery via the oral cavity may also minimize inter- and intra-subject pharmacokinetic variability related to stomach-emptying time, food effects, and enzymatic or chemical degradation in the gastrointestinal tract. The main characteristic of the technology is the delivery of solution formulations of API to the oral cavity in the form of a spray. However, many APIs are bitter or have other undesirable taste characteristics that need to be masked in order to develop palatable, patient-acceptable drug products. The following discussion will review the approach for developing a palatable oral spray for a model API.

DEVELOPING PALATABLE DRUG PRODUCTS – A STAGED APPROACH

The development of palatable drug products can be a daunting challenge. This is exacerbated by the general misconception in the pharmaceutical industry that taste perception cannot be quantified. Nothing could be further from the truth – sensory science is a core competency of most consumer packaged goods companies that compete on the basis of product aesthetics. Pharmaceutical companies, of course, have the added complexity of managing human exposure to drug substances, which is their core competency.

It is nearly impossible to develop a palatable drug product without knowing the taste characteristics of the API. Accordingly, Senopsys LLC followed the two-stage Taste Assessment and Taste Optimization development approach described herein.

STAGE I – TASTE ASSESSMENT

The objective of this assessment was to develop the dose-response function for the model API in an

unflavored, unsweetened oral spray excipient system composed principally of solubilizers. Five doses were dispensed in a fixed-dose volume of two 100 microliter actuations to deliver 1, 2, 4, 6, and 8 mg. This dose volume was set to maximize residence time in the oral cavity and minimize the swallowing reflex. At this volume, the upper end of the dose-response was bound by the solubility of the API.

Taste Profiling Procedure

The oral sprays were evaluated by trained and experienced pharmaceutical sensory panelists using the Flavor Profile method of descriptive sensory analysis.¹ Flavor Profile entails the identification and measurement of the sensory attributes of products, eg, texture, aroma, taste, and mouthfeel. Reference standards are used to define the attributes, and reference scales for intensity of different attributes ensure consistent application of the measurements across panelists and reproducibility across evaluations.

Both the initial flavor and aftertaste characteristics of drug products are important determinants of

patient acceptability; therefore, it is critical that each be evaluated. Following two spray actuations directed to the tongue, the initial flavor characteristics were measured during the first 10 to 20 seconds. The aftertaste characteristics were measured at eight time intervals (1, 3, 5, 10, 15, 20, 25, and 30 minutes).

The drug product was under an Investigational New Drug application and accordingly, the study was conducted under the auspices of an external Institutional Review Board.

Dose/Response Results

The challenge for many drug products is to mask the undesirable sensory characteristics of the API and excipients in the initial flavor and throughout the aftertaste (eg, bitterness, burn, stinging, and drying). Visualizing the data as a function of time provides valuable diagnostic information (Figure 1). A series of time-intensity plots were prepared for the critical sensory attributes. In each time-intensity plot, the area above a slight intensity on the Flavor Profile scale (>1) has been shaded. Based on experience across a

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wide range of drug products, undesirable characteristics above a slight intensity are clearly perceptible to most patients and are often found to be unacceptable. To increase patient acceptability, the intensity of the undesirable characteristics should remain below 1 throughout the product's flavor profile. Conversely, favorable attributes (eg, sweetness and flavor aromatics) should remain above this slight intensity throughout the product's flavor profile.

The bitterness profiles of the five doses delivered as oral sprays varied significantly over the study dose range as shown in Figure 1. As expected, the perceived bitterness increased with increasing API dose. The bitterness was found to linger at clearly perceptible levels for about 5 minutes at the lowest dose to about 20 minutes at the highest dose. The lingering bitterness of the API, represented by the relatively flat decay curves, poses a significant taste-masking challenge, particularly at the higher doses. The bitterness profiles of the 6-mg and 8-mg doses were similar, suggesting that these concentrations are approaching the upper plateau of the typical sigmoid taste-response curve.

Four other critical sensory attributes were identified and quantified - solvent aromatics and three mouthfeel factors (warming, tongue sting, and drying). The perceived intensity of these four attributes was found to be largely independent of API dose, which suggests they arise from the base excipient system. The time-intensity profiles for the critical attributes are shown in Figure 2 for the 8-mg dose.

The solvent aromatics were moderate in intensity initially but short lived, decreasing below a slight intensity by 3 minutes. The excipient system produced a warming mouthfeel, which had a profile similar to the solvent aromatics and a slightly lower tongue sting profile. The drying mouthfeel did not arise immediately as the maximum intensity did not occur until one minute - this is not uncommon for some mouthfeel

perceptions, including drying, numbing, and cooling.

Based on the Flavor Profile results, it was clear that the primary taste-masking challenge for this oral spray drug product was the bitterness profile of the API itself. The base excipient system contributed

other effects, but these were clearly secondary in importance from a taste-masking challenge. In order to produce a meaningful reduction in the perceived bitterness of the spray product, the concentration of the API would need to be reduced by 50% or more, ie, ≤ 2 mg per

FIGURE 1

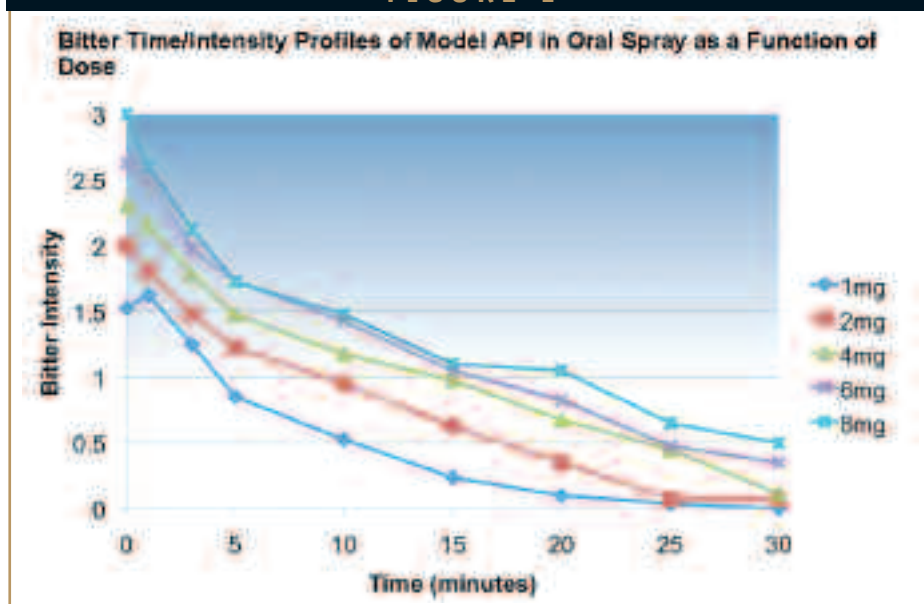
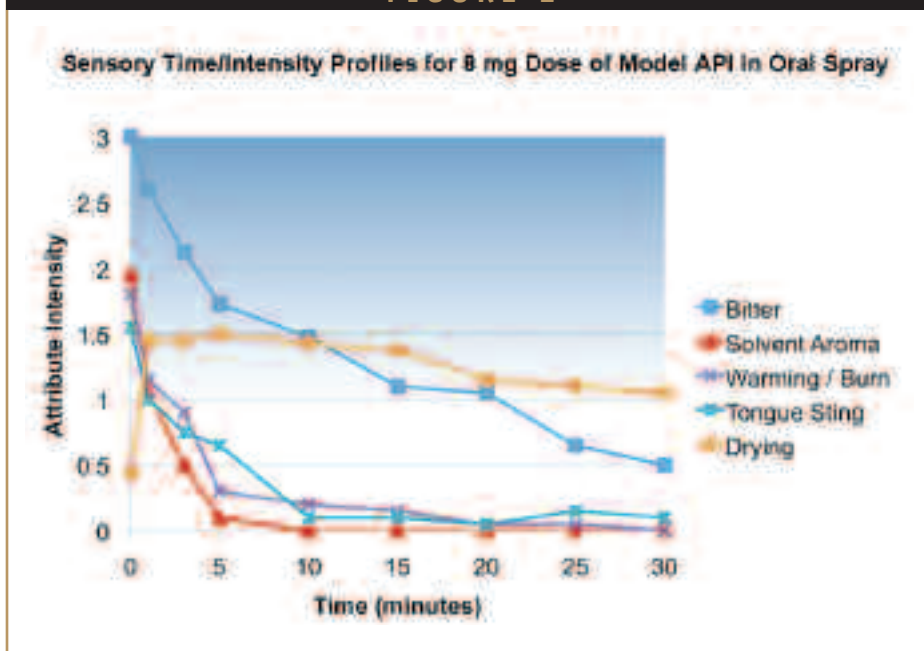


FIGURE 2



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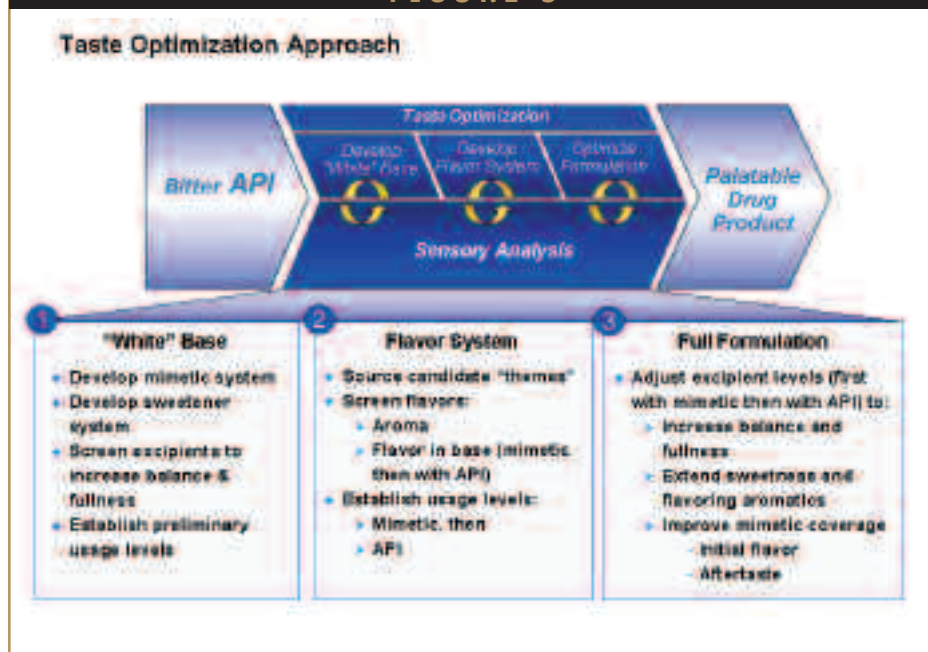
100 microliters. However, decreasing the concentration would necessitate increasing the number of spray actuations, which was viewed as negating the convenience of the oral spray and potentially impacting dosing compliance.

STAGE II – TASTE OPTIMIZATION

The objective of this stage was to develop a series of palatable oral spray prototype formulations containing the model API at 4 mg per 100 microliters

delivered in two actuations. Though the 8-mg dose poses a significant taste-masking challenge, this dose was selected based upon dose volume and solubility limitations.

FIGURE 3



Developing a Palatable Oral Spray Drug Product

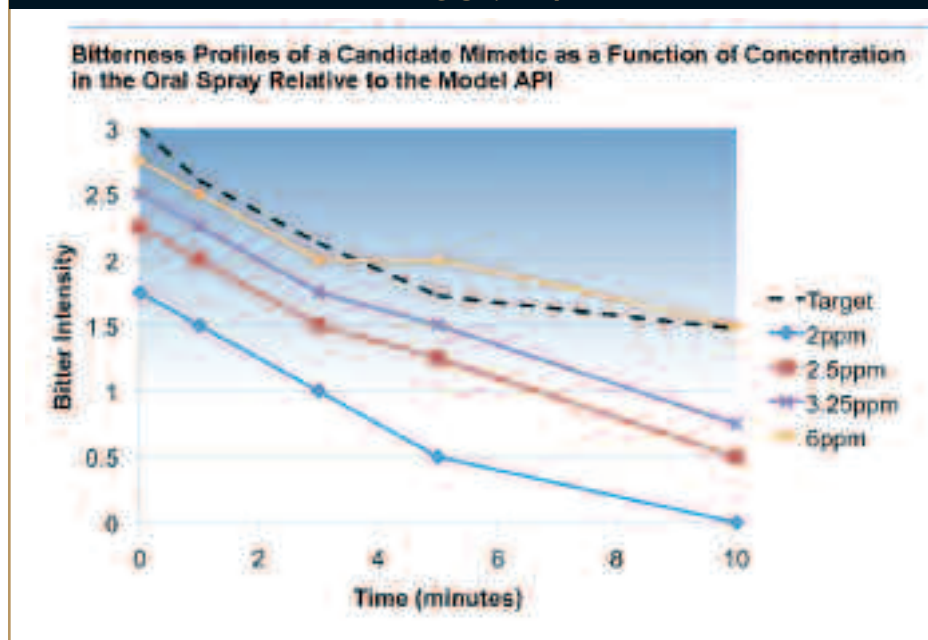
The palatability of a drug product is related to the perceived blend of the product's sensory characteristics. The model API was strongly bitter and lingered for several minutes in the aftertaste. This bitterness would be expected to "stand out" from the other basic tastes (sweet, sour, and salty). If the basic tastes can be balanced, then the bitterness of the drug substance may not be distinctly perceived, and the drug product may be more palatable. In general, this requires that the positive sensory attributes of the flavor system, specifically sweetness and flavoring aromatics, be perceived at a stronger intensity than the negative sensory attributes (eg, bitterness).

The process shown in Figure 3 was followed to develop a series of palatable oral spray formulations for the model API. This approach has been adapted from the consumer packaged goods industries where product aesthetics are critical to commercial success and has been used to develop dozens of palatable oral drug products. The first step was to develop a "white" placebo base for the oral spray. A "white" or unflavored base exhibits balanced basic tastes (sweet, sour, salty, and bitter), which, as previously mentioned, is the underpinning of taste-masking. In this case, the objective was to "blend away" the bitterness of the API and to a lesser extent the aromatics and mouthfeel effects of the excipient system.

Identify a Mimetic

To reduce human exposure to drug substances during development, the first step was to develop a mimetic system using Generally Recognized as Safe

FIGURE 4



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(GRAS) or FDA-approved excipients that closely match the critical sensory attributes of the API. For the model API, the goal was to identify a mimetic and usage level that would replicate the bitterness profile of the 8-mg dose as shown in Figure 1. There are numerous compounds that are bitter, including caffeine, sucrose octaacetate, quinine sulfate, naringin, magnesium sulfate, and denatonium benzoate. Each has a different bitterness profile. Several bitter mimetics were formulated in the base excipient system and evaluated by the sensory panelists following the same evaluation protocol used in Stage I. The resulting bitterness profiles were compared to that of the model API. The usage levels were adjusted and the bitterness profiles iteratively generated until a bitterness profile close to that of the model API was attained. The bitterness profiles for one mimetic are shown in Figure 4 as a function of concentration in the oral spray excipient system. Based on these results, the mimetic concentration of six parts per million (w/w) was selected for use in developing a series of palatable oral sprays.

Develop the Sweetener System

The next step was to develop a sweetener system with a sweetness profile that closely matches the bitterness profile of the model API in the base excipient system. There are numerous sweeteners available to formulators - nutritive, sugar alcohols, and high intensity (artificial). The concentrations required for nutritive sweeteners or sugar alcohols exceeded the usable range for the oral spray dosage form. As a result, only the high-intensity sweeteners were considered.

The candidate high-intensity sweeteners were first evaluated individually in the base excipient system to determine if they provided ample sweetness. Several could not provide the target level of sweetness without distorting the flavor profile with increased bitterness

and metallic aromatic off-notes, and were subsequently eliminated. Appropriate combinations of high-intensity sweeteners were then considered to achieve the desired sweetness impact and duration. The sweetness profiles of four sweetener

systems are shown in Figure 5.

The leading sweetener system was then combined with the mimetic and the usage level optimized. The results are shown in Figure 6. The sweetener system produced the intended effect of reducing

FIGURE 5

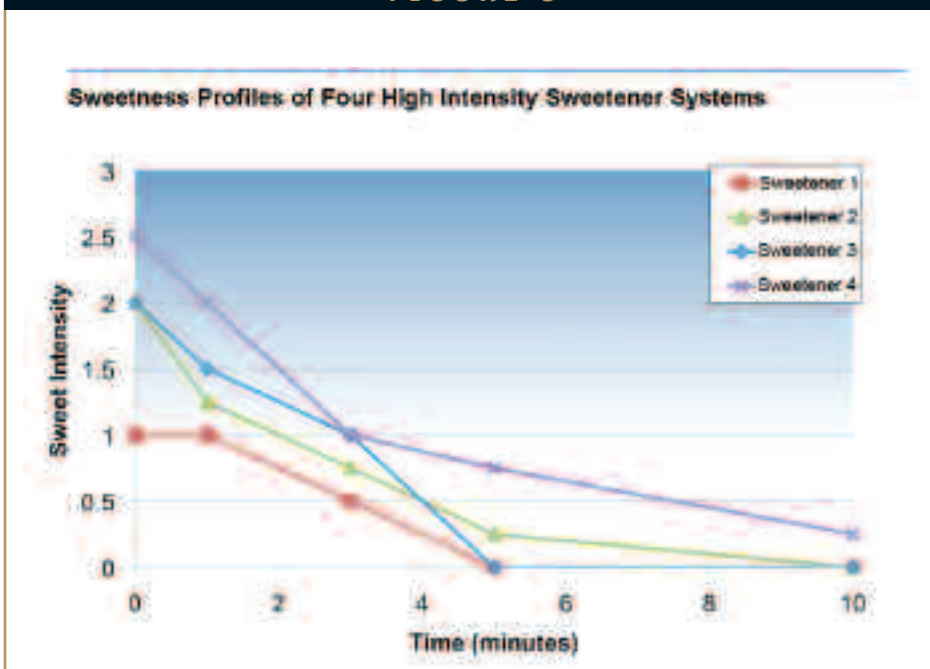
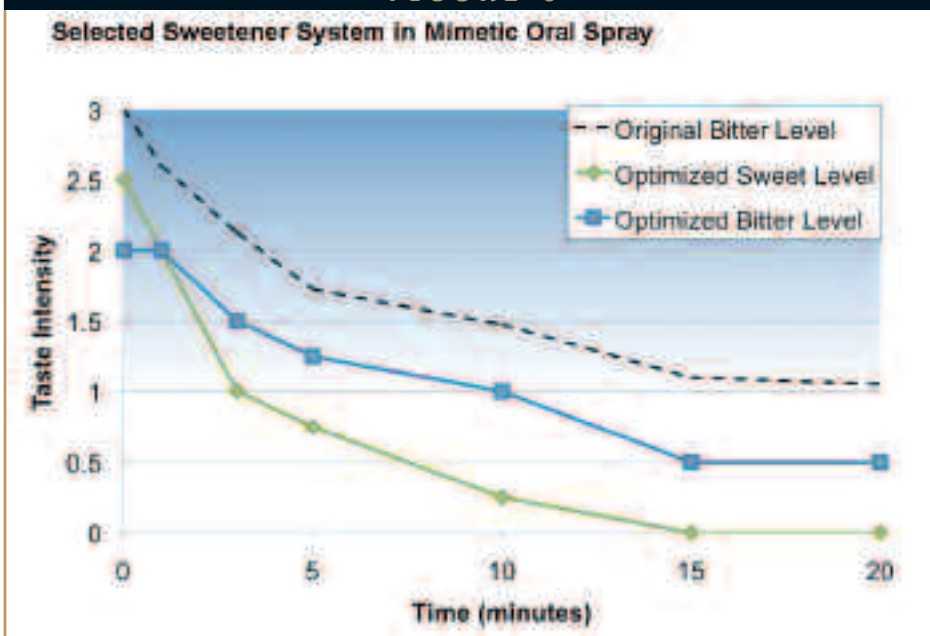


FIGURE 6



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the bitterness profile of the mimetic. The sweetness profile was somewhat lower than the bitterness profile and therefore suboptimal; however, further increases in sweetness had the same deleterious distortion of the Flavor Profile previously described.

There are numerous excipients that can be used to modify specific sensory characteristics of drug products. For example, sodium chloride is used to blend or balance basic tastes. Menthol can be used at sub-odor threshold levels to provide a cooling mouthfeel that can be beneficial in certain applications. Monoammonium glycyrrhizinate is sometimes used to extend and support sweetness in the aftertaste. There are several suppliers and grades of monoammonium glycyrrhizinate, and the

effects in different systems can vary significantly, sometimes adversely affecting palatability. Several flavor modifiers were explored in the mimetic placebo base; the results are shown in a series of plots in Figure 7.

Three plots are shown in Figure 7. The left chart represents the “control” with no addition of the flavor modifier (same as shown in Figure 6). The middle chart represents a low usage level of the flavor modifier, and the right represents a high-usage level. As shown, the upper usage level increased the initial bitter intensity and did not compensate with increased sweetness. The lower usage level increased the sweetness profile without increasing the bitterness, illustrating that more was not necessarily better.

It was advantageous at this point of

development to verify that the results obtained using the mimetic translated well to the model API. This was accomplished by evaluating the API-containing prototypes and making any necessary adjustments to the formulations owing to perceived differences between the performance of the mimetic and API.

Develop & Optimize the Flavor System

The next step was to develop the flavor system. The objective was to improve the coverage of the undesirable critical sensory attributes in the initial flavor and aftertaste by building a well-blended and full-bodied flavor. The structured approach shown in Figure 3 was followed to select flavoring ingredients.

The first step was to select appropriate flavor “themes” based on the market image profile for the drug product. In this case, the drug product was indicated for adults; therefore, pediatric flavors, such as bubblegum, were eliminated from consideration. Additionally, the drug product was intended for worldwide marketing, which required that the flavor have widespread appeal, eliminating esoteric flavors like honey, guava, or green tea.

Candidate flavoring materials were sourced from reputable suppliers, screened in aroma, and formulated into the mimetic placebo base at appropriate initial usage levels. Flavor Profile analysis was conducted to measure key attributes, such as aromatic identity and intensity, balance (blend) and fullness (complexity), lingering flavor, and mouthfeel characteristics.

The final step was to optimize the usage levels of all excipients, using designed experiments as appropriate and sensory panels evaluating the resulting prototypes for the aforementioned attributes. The excipient levels were then adjusted to further improve the balance and fullness of the final drug product. The sensory performance of the leading

FIGURE 7

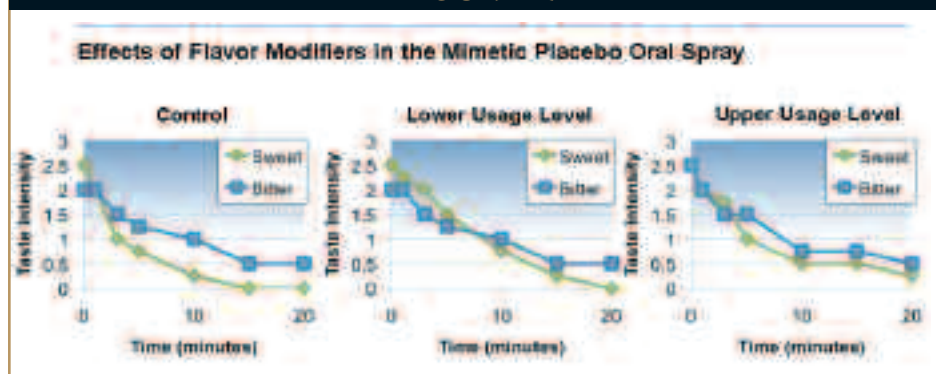
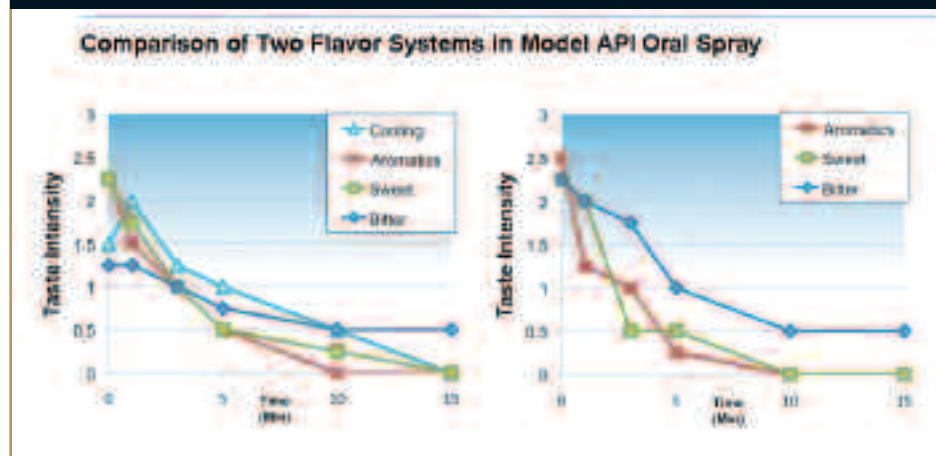


FIGURE 8



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flavored formulations were verified in the API-containing drug product, and final adjustments were made to account for perceived differences between the API and mimetic.

In an effort to minimize the likelihood of chemical or physical instability, several different flavor systems were developed, each of which is expected to be patient-accepted based on overall palatability. Most importantly, the bitterness profile of each formulation was significantly reduced, and all exhibited ample initial and lingering sweetness. The flavor identity of each formulation was appropriate in impact and duration for the target patient population. The overall flavor profile was well blended such that no individual sensory characteristic “stood out” from the others. In some systems, the addition of low levels of mint produced a beneficial cooling mouthfeel and postponed the bitter breakthrough (bitter intensity rising above the sweet intensity). An example of this is shown in Figure 8. Selected formulations were placed on stability according to ICH guidelines to assess chemical and physical stability. Formulations were determined to be chemically and physically stable for up to 3 months.

SUMMARY

Oral spray drug delivery technology is capable of addressing unmet needs for a broad array of existing and future pharmaceutical products. In addition, palatable drug products improve the prospects for patient compliance and adherence. The sensory-directed formulation development approach described herein has been shown to yield a palatable oral spray product for an extremely bitter API.

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BIOGRAPHIES



Jeffrey H. Worthington is President and Founder of Senopsys LLC, a specialty services firm dedicated to the development of palatable pharmaceuticals. He has more than 20 years of experience in taste assessment and optimization and has contributed to the development of numerous prescription and OTC medications. Mr. Worthington is a frequent author and speaker on the subject of developing palatable pharmaceuticals and serves on the NIH's Best Pharmaceuticals for Children Act - Pediatric Formulation Initiative. Prior to founding Senopsys, Mr. Worthington was Vice President of Pharmaceutical Technology at Arthur D. Little, Inc. He earned his BS in Chemistry from Northeastern University and his MBA from Babson College.



David A. Tisi is Technical Director at Senopsys LLC. Mr. Tisi is a trained descriptive sensory panelist and formulator with experience developing palatable foods and pharmaceuticals. Having spent his career at the intersection of food and pharmaceutical technology, he has particular expertise in applying food technology to the development of novel pharmaceutical dosage forms. Prior to joining Senopsys, he was a Scientist at TIAx LLC, where he managed and executed projects to improve the sensory quality of food and drug products. Mr. Tisi earned his MS in Food Science from Cornell University.



Dr. Frank E. Blondino is Executive Director of Formulation and Process Development at NovaDel Pharma Inc., a specialty pharmaceutical company developing oral spray formulations of a broad range of marketed therapeutics. Dr. Blondino has 13 years of experience in developing pharmaceutical products, including parenterals, inhalation aerosols, and oral sprays. Immediately prior to joining NovaDel, he was Associate Professor/Associate Director for Development Research in the Department of Pharmaceutics at Virginia Commonwealth University. He has also held positions at Magellan Laboratories, Baker Norton Pharmaceuticals, and Hoechst Marion Roussel. Dr. Blondino is co-inventor on more than a dozen patents and applications. He earned his BS in Pharmacy and his PhD in Pharmaceutics from Virginia Commonwealth University and is a licensed pharmacist.



Dr. Foyeke O. Opawale is Manager, Formulations Development at NovaDel Pharma Inc. Dr. Opawale has more than 10 years of experience in the research, development, and manufacturing of drug products and has held positions at different types of pharmaceutical companies, including OTC, biotech, generic, and specialty companies. She earned her BPharm from Obafemi Awolowo University, Ile-Ife, Nigeria, and her PhD in Pharmaceutical Sciences (Pharmaceutics) from the University of Connecticut. During her career, Dr. Opawale has gained extensive experience in the development of new liquid formulations for oral and transmucosal drug delivery, the formulation of topical drug products, development of conjugated protein formulations (liquid and solid dosage forms) for enhanced oral absorption, predicting emulsion stability from the investigation of interfacial properties of emulsifiers or surfactants, and microencapsulation via complex coacervation. She is a co-inventor on five patents and applications.

DRUG DELIVERY

Executive



Randy Bull, PhD
Global Business Director,
EUDRAGIT®

Pharma Polymers
Evonik Degussa
Corporation

"We have expanded our value chain to match that of our customers. With a global presence, we offer customers one source of support, from feasibility demonstration to proof-of-concept for complex oral drug delivery. Providing a means to reduce early stage development time can help our customers accelerate their product development."

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Development**

**Proof of
Concept**

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Services**

**Advanced
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PHARMA POLYMERS: NEW SOLUTIONS FOR THE DRUG DEVELOPMENT VALUE CHAIN

Evonik Industries is a global market leader in specialty chemicals, offering the broadest portfolio of products and services in the regulated pharmaceutical markets. Pharma Polymers is a business line of Evonik Degussa Corporation. Its EUDRAGIT® acrylic polymers are used in the manufacturing of enteric coatings on solid dosage forms, sustained-release formulations, and immediate-release applications. Pharma Polymers is committed to providing solutions to the pharmaceutical and biopharmaceutical industry in drug development, drug delivery, and manufacturing with products and services that meet requirements throughout the drug development process - from excipients for drug formulations to drug delivery technologies. Drug Delivery Technology recently interviewed Randy Bull, PhD, Global Business Director EUDRAGIT Polymers, to discuss how Pharma Polymers is working with customers to meet drug delivery challenges in the global market.

Q: What is the focus of Evonik Pharma Polymers?

A: Historically, our market focus has been primarily in modified-release solid oral dosage forms. However, the unique functionality of EUDRAGIT polymers has also resulted in significant transdermal and topical applications. While solid orals remain the primary focus, we find that we must move further into the value chain of the market - into solving unique, more challenging delivery mechanisms and release profiles of pharmaceutical companies. This leads us to evaluate alternatives different from our conventional approach.

Internally, Pharma Polymers remains uniquely placed in the pharmaceutical ingredient market. While part of a larger chemical company, our manufacturing processes and quality systems have been dedicated only to pharmaceutical applications, enabling us to provide products within increasingly challenging regulatory

requirements. We support and comply with key IPEC excipient manufacturing guidelines and are proud of the successful audits our customers have conducted.

Q: What are some of the key challenges emerging for the pharmaceutical industry, and how are you addressing those challenges?

A: The pharmaceutical industry is facing significant technical challenges, among many others, from discovery to the market. Often those technical challenges reach into their supply chain, and we have had to adapt our polymer and application development to address these issues where we can. This again requires us to touch new elements within a pharmaceutical customer value chain.

As an example, a well-known problem with many new molecules coming from discovery is

DRUG DELIVERY *Executive*

one of solubility and bioavailability. EUDRAGIT polymers can address solubility enhancement depending on the formulation and production process; however, this goes well beyond the traditional coating area. Methacrylic acid copolymers have been shown to offer superior stability for solid dispersions of drugs in a polymer matrix. Therefore, we have invested in advanced processes that can effectively achieve a solid dispersion of drug in polymer, such as melt extrusion and spray drying. The resulting increase in drug solubility can have a beneficial effect on bioavailability.

Q: How else do you see these challenges affecting your business?

A: The functional demand on polymer formulations has become more complex in order to meet specific release profiles that influence therapeutic value of the drug molecule. EUDRAGIT enteric polymers have long been an industry preference for enteric drug delivery. But “enteric” has often been a relatively simple definition defined by USP requirements.

Now, to help enhance bioavailability, pharmaceutical companies have been evaluating regional absorption windows to see where drugs are best absorbed in the gastrointestinal tract. The range of EUDRAGIT polymers available, and their ability to be mixed in various ways, offers a mechanism for pH-based GI targeting. A formulator

can now create a formulation that will release the drug selectively within the part of the GI tract where maximum absorption takes place. Now, consider the advantage of combining GI targeting with solubility enhancement by melt extrusion, and you can see the potential.

Q: What regulatory changes do you see affecting the excipient business?

A: The regulatory environment has many changes that are and will change the landscape for excipient companies. In modified release, an interesting development is the focus of the US FDA on the effects of ethanol on drug ingestion. For those companies relying on coating with cellulose and methacrylic acid polymers for sustained release, it turns out that coating systems can be vulnerable to alcohol, and may lead to dose dumping.

Therefore, we have been investigating alternatives to coating. In both solid and dispersion forms of EUDRAGIT polymers, we have found that polymer matrix formulations offer dosage forms that are rugged in the presence of alcohol. This matrix formulation concept also results in rugged formulations for other polymers systems as well, so we and others in the excipient industry all have had to adjust our approach to formulation - more matrix formulations as opposed to coating for sustained release. Via certain formulation approaches, however,

we also have found EUDRAGIT sustained-release polymers to be resistant to ethanol in coating systems.

Q: How have drug delivery needs and industry changes affected the business model for Evonik Pharma Polymers?

A: Throughout the past several years, we have been moving further into the pharmaceutical industry value chain by moving beyond polymer supply and basic technical support. We still do that, but now we must do much more to provide what our customers in the pharmaceutical industry demand.

One change is simply our geographic presence. As the pharmaceutical industry becomes more global, we have also invested in a larger global presence. We now have fully equipped technical service laboratories in five regions, including Germany, the United States, India, China, and Japan, and have built strong regional sales and marketing platforms around each of those laboratories to provide regional response to our customers. At the same time, these laboratories become a linked global resource.

One result of these globally networked organizations is that when a pharmaceutical company is developing a product in one region for ultimate production in another region, we essentially have local support at both the development site and technical transfer to the production location. The global

DRUG DELIVERY *Executive*

expansion has been successful to the point that we recently doubled the size of our laboratory in India, which now serves as a global R&D resource as well as a regional technical service laboratory.

Q: Your value chain concept suggests more than basic technical support. Can you explain what Pharma Polymers is doing beyond that?

A: The investment in our service offering to the industry has increased. One example is taking on more of a development role with our customers in the somewhat specialized modified-release applications. While the pharmaceutical industry knows best what their development challenges are, our long history and experience in the use of EUDRAGIT polymers in modified release enables us to know best how to apply them to achieve drug-release targets. With our experience, one result can reduce development time in the early stages of formulation development. We can quickly carry out feasibility demonstration.

We do not have to stop there. Our investment in GMP capabilities in Germany allows us to work on formulation development all the way through the early clinical phases. This can significantly reduce time and costs at this stage of development because it avoids the time and difficulties of managing tech transfer as the project moves through these development stages.

Q: Can you explain how platform drug delivery technologies factor into your strategy?

A: Essentially, everything we do with our functional EUDRAGIT polymers is drug delivery. Whether it is simply taste-masking or moisture protection, GI targeting, or sustained release, we are modifying the delivery of the drug to result in a certain release characteristic. The ultimate "solution" in this process is helping a pharmaceutical customer be successful in finding a truly enabling approach to delivering the desired drug-release profile that otherwise is not achievable. In our R&D, we have identified some approaches to use our polymers that can be enabling in certain situations, and we believe those technologies offer platform drug delivery technologies to the industry. We've branded three of those platforms - EUDRAMODE®, EUDRAPULSE®, and EUDRACOL® - and where appropriate, we conduct the development and offer licenses to these platforms.

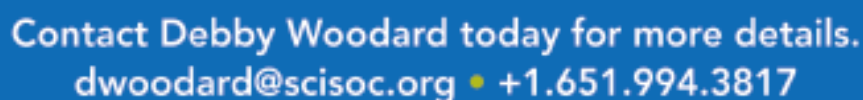
However, at the end of the day, we must meet drug delivery challenges as simply and efficiently as possible. When working along with our customer at the basic feasibility demonstration stage, we begin seeking a solution at the most basic level, depending on the target. When we find a solution, we move on. But if the target is suitably challenging, we try to work until the target is met and want to reach proof-of-concept as quickly and efficiently as possible.

Q: What kind of working relationships become necessary to implement the value chain model?

A: We offer flexibility in our business relationship with the pharmaceutical company, and it is based on the challenge and complexity of the result that we must deliver. Right now, we have development projects in our laboratories that are short-term feasibility demonstrations that we can execute quickly. Often, a simple confidentiality agreement provides sufficient basis for the project.

However, we also are engaged at the other end of the value chain, where we are in long-term development toward a unique delivery target. In such cases, detailed milestone-based development agreements can be necessary to adequately reflect the risk both we and our customer are making to achieve the goal. Our development models at the extreme and in between are structured to the situation. We can't be successful in our growth without helping our customers achieve their objectives. ♦

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TECHNOLOGY Showcase

INHALATION & TRANSDERMAL DELIVERY

Enabling your success

3M Drug Delivery Systems

3M Drug Delivery Systems partners with pharmaceutical and biotech companies to team your molecules with our inhalation or transdermal drug delivery technology. 3M offers a full range of feasibility, development, and manufacturing capabilities combined with regulatory guidance to help get your product to market. In-house resources, including toxicology, regulatory expertise, quality assurance, operations, and marketed product support, are available for each step of the development and commercialization process. To learn more about our latest developments and newest technologies please stop by Booth No. 1725 while attending AAPS. For more information, contact 3M Drug Delivery Systems at (800) 643-8086 or visit www.3m.com/dds.

LICENSING OPPORTUNITIES



Aveva has numerous products for license from its development pipeline along with a full complement of R&D capabilities to produce transdermal drug delivery systems that fortify R&D pipelines and maximize product life cycles. Aveva Drug Delivery Systems is one of the world's largest manufacturers of and a pioneer in transdermal drug delivery systems of providing pharmaceutical partners with fully integrated, controlled-release transdermal products that fulfill unmet market needs. Products for licensing include Sufentanil, Fentanyl, Clonidine, and Nicotine. For more information, contact Robert Bloder, VP of Business Development, at (954) 624-1374 or visit www.avevadds.com.

DEVELOPMENT SERVICES

Azopharma
Product Development Group

The Azopharma Product Development Group of companies provides total product development, helping you Turn Ideas Into Cures™. Azopharma provides the full spectrum of development services from preclinical assessments to commercialization. Our goal is to help maximize your financial resources by accelerating your timelines. Our proprietary Phase I Express™ process is designed to accelerate your drug development by leveraging our ability to manage the execution of multiple projects along parallel timelines. Azopharma provides formulation services in a variety of dosage forms and in support of preclinical and clinical studies. Starting with Phase I, we can manufacture your clinical trial material as well as conduct the clinical trials, including analytical support. For more information, contact Azopharma at (954) 433-7480 or visit www.azopdogroup.com.

EXCIPIENT BOOK



Among synthetic excipients, polyvinylpyrrolidone, marketed under the brand name Kollidon®, is one of the most important substances in the pharmaceutical industry. Starting from soluble Kollidon grades that were synthesized by W. Reppe in 1939, a number of products followed, including insoluble grades, copolymers, and sustained-release preparations for numerous applications. Although the products are included in all relevant pharmacopoeias, there is a need for a detailed description with special emphasis on their

technological properties and applications. This 9th edition of the *Kollidon®-Book* provides answers to all questions relevant to product properties, stability, analytical methods, toxicological data, pharmacopeial status, and applications of Kollidon. You can order your personal copy of the *Kollidon®-Book* free of charge by e-mail at tina.massholder@basf.com.

TECHNOLOGY Showcase

PREFILLABLE DELIVERY SYSTEMS



BD Medical - Pharmaceutical Systems is dedicated to developing prefilled drug delivery systems designed to fit the needs of the pharmaceutical industry. Whether a glass or plastic

prefillable syringe, a nasal spray system, a dry drug reconstitution system, an injection or self-injection device, BD Medical - Pharmaceutical Systems provides the expertise and experience required by the pharmaceutical industry in a packaging partner. We deliver cost-effective alternatives to conventional drug delivery methods, which differentiate pharmaceutical products and contribute to the optimization of drug therapy. All of its prefilled devices are designed to meet healthcare professionals' demands for safety and convenience and to fulfill patients' needs for comfort. BD's worldwide presence, market awareness, and pharmaceutical packaging know-how allow it to propose suitable solutions for all regional markets and parenteral drug delivery needs. For more information, contact BD Medical - Pharmaceutical Systems at (201) 847-4017 or visit www.bdpharma.com.

CAPSULE FILLING & SEALING



Designed to allow formulation scientists the ability to better exploit the potential of lipid-based formulations for poorly soluble compounds, the CFS 1200 helps accelerate the development

timeframe and achieve Faster Time to First in Man. A fully automatic cGMP-compliant machine, it fills and seals up to 1,200 capsules per hour with liquid or semi-solid formulations without banding. It is designed for ease-of-use and high reliability, with the ability to quickly clean and change capsule sizes with available change parts. Product integrity is ensured with gentle handling of capsules before sealing and during the drying cycle. Other features include a robust filling pump with highly accurate temperature control, improved capsule manipulation before sealing and during drying using new "Cap-edge" handling system, and improved design of filling and sealing process that ensures better control and cleanliness. For more information, contact Capsugel at (888) 783-6361 or visit www.capsugel.com.

CLINICAL SERVICES & SUPPLIES



Bilcare Global Clinical Supplies serves the Americas, Europe, and Asia with clinical trial materials support, services, and complete project management. Its

services for solid, semi-solid, liquid, DEA (CI-V), and biotech clinical trial materials (CTM) satisfy a broad range of requirements from preformulation research and development, manufacturing, analytical services, and clinical supplies packaging and labeling, to IVRS, QP services, controlled temperature (cold and frozen chain) CTM storage, distribution worldwide, and returns and destructions accountability. Our integrated approach provides you with seamless service throughout your entire project. We combine our industry experience and our total clinical supply chain service and delivery to provide smart, efficient, and innovative solutions. For more information, contact Bilcare Global Clinical Supplies at (610) 935-4300 or www.BilcareGCS.com.

PHARMACEUTICAL SOLUTIONS



Catalent Pharma Solutions' services include a full range of development services, such as preclinical support, API development, analytical services, drug delivery development, clinical manufacturing, and packaging services. We have expertise in inhalation development and can offer innovative biologic cell-line development using our proprietary GPEx™ technology. Catalent's drug delivery systems include soft gelatin and Vegicaps® Soft capsules; Zydis® fast-dissolve dosage form; oral modified-release technologies, including EnCirc®, EnVel®, and EnSolv®; and a range of inhaled technologies. Along with our proprietary dose forms, we also manufacture traditional oral, sterile, topical, and inhaled dose forms. We also produce biologics for preclinical and clinical studies. Globally positioned, our packaging services include commercial packaging for all dose forms and the supply of printed components. For more information, contact Catalent Pharma Solutions at (866) 720-3148 or visit www.catalent.com.

TECHNOLOGY Showcase

TOPICAL FORMULATIONS



When you work with Dow, you can feel comfortable in knowing that your product is in very experienced hands because we focus only on topical formulations. After 31 years, we know how to prevent the unique problems that often occur during topical formulation development, analytical method development, scale-up, and long-term storage. In just the past 3 years alone, we helped 65 clients develop stable, elegant, scalable formulations that are disease compatible and penetrate the skin or ocular tissue as required. This is accomplished by a team of formulation, analytical, and drug transport scientists using Dow's unique formulation development process. For more information, contact Dow Pharmaceutical Sciences, Inc. at (707) 793-2600 or visit www.dowpharmsci.com.

DEVELOPMENT & MANUFACTURING



DPT is a contract development and manufacturing organization (CDMO) specializing in semi-solid and liquid dosage forms. DPT provides fully integrated development, manufacturing, and packaging solutions for biopharmaceutical and pharmaceutical products. DPT is the industry source for semi-solid and liquids — from concept to commercialization and beyond. Drug development services range from preformulation, formulation and biopharmaceutical

development, analytical development, and validation through process development. Production capabilities include four cGMP facilities, clinical trial materials, full-scale commercial production, controlled substance registration Class II-V, and complete supply chain management. Packaging services encompass engineering and procurement resources necessary for conventional and specialized packaging. For more information, contact DPT at (866) CALL-DPT or visit www.dptlabs.com.

CUSTOM MANUFACTURING



DSM Pharma Chemicals, a business unit of DSM Pharmaceutical Products, is a global provider of custom manufacturing services to the

pharmaceutical industry. Services include advanced intermediates, such as unnatural amino acids and derivatives, registered materials, and active pharmaceutical ingredients. Our technologies include biocatalysis, homogeneous catalysis, fermentation, and chiral technologies. DSM delivers comprehensive custom manufacturing services to the spectrum of pharmaceutical companies, including emerging pharmaceutical companies and large pharmaceutical companies. From clinical to commercial services, DSM focuses the right resources on providing the highest level of service and quality, while applying innovative solutions to satisfy customers' unique manufacturing needs. For more information, contact DSM Pharma Chemicals at (973) 257-8011 or visit www.dsmpharmaceuticals.com.

ORALLY DISINTEGRATING TABLETS



AdvaTab® is a new generation of ODT technology that offers distinct advantages and unique applications — unparalleled taste, flexible dosing, modified release, and a robust tablet. AdvaTab can be combined with Eurand's leading Microcaps® taste-masking technology

to provide an ODT with superior taste and mouth-feel. AdvaTab tablets dissolve rapidly in the mouth within 15 to 30 seconds, and the smooth mixture of carrier excipients and taste-masked drug granules is suitable for delivering high drug doses. Modified-release drug granules can also be incorporated into the AdvaTab dosage form to provide a fast-dissolve tablet with sustained-release properties. AdvaTab tablets can be packaged in either bottles or push-through blisters. For more information, contact Eurand at (937) 898-9669 or at partners@eurand.com.

TECHNOLOGY Showcase

PHARMA POLYMERS



Evonik Industries is a global market leader in specialty chemicals, offering a broad portfolio of products and services to meet the drug delivery challenges of the pharmaceutical market. Evonik Pharma Polymers manufactures EUDRAGIT® acrylic polymers used for enteric, sustained-release, and protective formulations. The unique functionality of EUDRAGIT polymers can also meet high sophisticated drug delivery requirements (eg, pulsed drug release). We have adapted our services to meet the requirements of the pharmaceutical industry's value chain. As a result, we are able to support our

customers in the development process to bring products safely and quickly to the market. From excipients supply to the development of custom tailored drug delivery solutions, our customers benefit from our knowledge and expertise. For more information, contact Evonik Degussa Corp., Pharma Polymers at (732) 981-5383 or visit www.eudragit.com.

SOLVENT-FREE ADSORPTION



Designed for enhancing the solubility of poorly soluble drugs in solid dosage forms, this technique allows the transformation of liquid or semi-solid lipid formulations into solid particles that can subsequently be filled into hard shell capsules or alternatively compressed into tablets. The active may be dissolved or dispersed in the formulation prior to adsorption onto a solid neutral carrier, such as calcium silicate, with the aid of conventional mixers. The success of the technique depends much upon the properties of the carrier, notably its flow characteristics and capacity to absorb the desired amount of formulation. Our laboratory has successfully loaded up to 68% liquid SELF onto solid support. For more information, contact Ron Permutt of Gattefosse at (201) 265-4800 or visit www.gattefosse.com.

OLIGONUCLEOTIDE-BASED DELIVERY



Due to the many challenges facing the delivery of RNA and DNA derivatives into cells, Genzyme Pharmaceuticals provides value-added solutions for delivering these oligonucleotide-based therapeutic actives using a unique combination of products, services, and technologies. Readily available products, such as synthetic phospholipids, cationic lipids, sphingolipids, and helper lipids can be used in liposomal and other lipid-based delivery systems. Through an integrated resource of custom manufacturing expertise

with core competencies in lipids, peptides, polymers, carbohydrates, lipo-peptides, and other small molecules, we provide high-quality, GMP excipients needed for cutting-edge oligonucleotide-based delivery systems. LipoBridge® and LipoMask™ are two proprietary drug delivery technologies that may be considered for oligonucleotide delivery. For more information, contact Genzyme Pharmaceuticals at (800) 868-8208 or pharmaceuticals@genzyme.com or visit www.genzymepharmaceuticals.com.

INNOVATIVE SYRINGE SYSTEMS



The Gerresheimer Group is the leading manufacturer of glass and plastic products for the pharmaceutical and life science industry. The product portfolio ranges from pharmaceutical vials to complex drug delivery systems. Gerresheimer is also known for excellence in the area of RTF® (Ready to Fill) syringes, which are supplied completely washed, siliconized, assembled, nested, packed in tubs, and sterilized to the

customers. A range of proprietary accessories, such as the rigid needle shield with thermoplastic elastomer (TERNS) and the tamper-evident Luer lock closure with twist-off motion (TELC), facilitate safety and convenience for the end-users of these syringe systems. Gerresheimer partners with customers worldwide to meet specific market needs. For more information, contact Burkhard Lingenberg of the Gerresheimer Group at +49 211 6181-250 or visit www.gerresheimer.com.

TECHNOLOGY Showcase

MANUFACTURER & API SPECIALIST



Hovione is a fine chemicals company that specializes in the process development and manufacture of active pharmaceutical ingredients and regulated intermediates. Dedicated to solving the problems associated with the industrial production of complex chemical

entities, the company's expertise in process chemistry and regulatory compliance to cGMP standards is based on more than 40 years of experience. Over that time, its ability to provide customers with timely solutions that are dependable and economical has given them a worldwide reputation for superior customer service. Hovione's business is 50% custom synthesis for large pharma and biotech companies and 50% generic products. More than half of today's sales consists of products launched less than 5 years ago. For more information, visit Hovione at www.hovione.com.

COMBINATION CAPSULE TECHNOLOGY



InnerCap offers an advanced patent-pending multi-phased, multi-compartmentalized capsular-based delivery system. The system can be used to enhance the value and benefits of pharmaceutical and biopharmaceutical products. Utilizing two-piece hard shell capsules, the technology offers the industry solutions to problems affecting pharmaceutical companies, patients, and healthcare providers. The delivery system will be licensed to enhance pharmaceutical and biopharmaceutical products. It is a very effective way to deliver multiple

active chemical compounds in different physical phases with controlled-release profiles. The delivery system provides the pharmaceutical and biopharmaceutical industries with beneficial solutions to the industry's highly publicized need to repackage and reformulate existing patented blockbuster drugs with expiring patents over the next 5 years. For more information, contact InnerCap Technologies, Inc., at (813) 837-0796 or visit www.innercap.com.

ULTRA-PURE CHITOSAN



KitoZyme offers KiOmedine, the first range of non-animal ultra-pure chitosan and services for medical devices and drug delivery systems. Manufactured from vegetal source and in accordance with cGMP, KiOmedine ultra-pure chitosan exhibits excellent reproducibility, constant quality totally independent of seasonal variations, traceability, no risk of allergenicity, along with competitive price. KitoZyme's product development team (7-person staff of PhDs and engineers) provides expertise in functionalization, processing, and formulation of biopolymers applied to health sciences. KitoZyme also offers contract services, co-development opportunities, and capabilities to support customers in bringing innovative products to the market in the fields of wound care, haemostatics, surgical aids, ophthalmics, tissue engineering, drug delivery systems, adjuvants for vaccination, or cell encapsulating material. For more information, contact KitoZyme at info@kitozyme.com or visit www.kitozyme.com.

AIRLESS BOTTLE



LABLABO's new EasyFoil bottle is fitted with a pouch consisting of an aluminum multilayer film rolled up and welded around a superior ring and an inferior cup, both produced in a thick plastic material. The film is composed of an exterior PET layer and an interior PP or PE layer wrapping a central aluminum layer of 12 microns in thickness. Depending on the nature of the product used, the internal layer choice will be PP or PE, the ring and cup being produced in the same material with a

sufficient thickness to provide a perfect barrier, especially against oxygen or UV. EasyFoil accepts the most viscous products (> 100.000 cps) and the most fluid (alcohol) and offers excellent restitution, the bottle could be used upside-down, precise dosage delivery, or containment of the pouch at a stand still position, an ideal packaging for transdermal applications. For more information, visit Lablabo at www.lablabo.com, or e-mail l.khoury@lablabo.fr.

TECHNOLOGY Showcase

DELIVERY & SPECIALTY PHARMA



Penwest has a clear, well-defined growth strategy: to leverage its strength in drug delivery and drug formulation to develop a portfolio of products targeting disorders of the nervous system. The company's current development pipeline includes products for the treatment of pain, epilepsy, Parkinson's disease, spasticity, and edema. It is continually evaluating new growth opportunities, both internally and externally.

During 2006, Penwest made important progress in pursuit of that strategy. Its key accomplishments included the approval and launch of Opana ER® by Endo Pharmaceuticals, development of its internal pipeline, and enhancement of its organizational capabilities and processes. For more information, contact Penwest at (845) 878-8400 or visit www.penwest.com.

NASAL SPRAY SYSTEM



The Pfeiffer Bidose nasal spray system offers the ideal solution when more medication is required than can be applied via one nostril. The system lends itself for example to the application of pain relief medication and vaccinations. It effectively provides the opportunity to dispense the contained amount of liquid equally into both nasal cavities so that more drug substance can be made available for absorption into the

system for a longer period of time. Medication dispensed through the Pfeiffer Bidose system does not come into contact with air prior to being dispensed and therefore remains uncontaminated during the entire shelf-life. Its uniquely consistent spray performance fulfils the need for optimal dispensing efficiency. For more information, visit Pfeiffer of America at www.pfeiffer-group.com.

KNOWLEDGE MANAGEMENT



PharmaCircle is an innovative knowledge management company specializing in the drug delivery, pharmaceutical, and biotechnology fields, with a current client base ranging from start-up life science companies to world leaders in Big Pharma. Clients choose PharmaCircle's services and content for its comprehensive technical (pipeline, products, molecule, and technology) and business (deals, acquisitions, royalty, licensing, drug revenues, market information, etc) related information and analysis, which are ideal for all segments of small and large companies. PharmaCircle helps facilitate product life cycle management (LCM), partnering, licensing, and competitive intelligence efforts as well as supplements internal efforts and costs at a fraction of the cost if performed internally. For more information, contact PharmaCircle at (847) 729-2960 or visit www.pharmacircle.com.

CONTRACT SERVICE PROVIDER

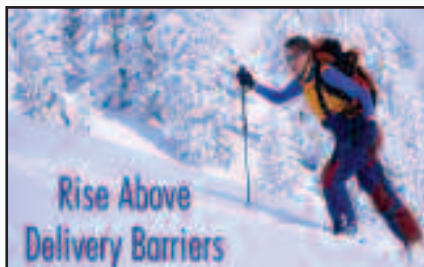


PharmaForm doesn't just provide its clients with creative solutions; it creates successful partnerships. As a pharmaceutical contract service provider, it offers a wide range of formulation, drug product development, manufacturing, analytical testing and stability services, patent litigation support services, and product platform licensing opportunities. Its formulation scientists have core expertise and experience in improving solubility of poorly soluble compounds. One such available technique to clients is Evaporative Precipitation into Aqueous Solutions (EPAS), a

process that causes the formation of nano-sized particles that can help enhance bioavailability of a poorly soluble compound. PharmaForm's state-of-the-art facility is registered with the FDA and the DEA and is cGMP/GLP Compliant. For more information, contact PharmaForm at (512) 834-0449 or visit www.pharmaform.com.

TECHNOLOGY Showcase

CONTROLLED DELIVERY PLATFORM



SCOLR Pharma applies its patented CDT® Controlled Delivery Technologies to develop formulations for companies with pharmaceutical, OTC, and nutraceutical products. These elegantly simple

technologies can be used for controlled-release periods for up to 24 hours and can be manufactured using readily available standard materials and conventional production equipment. SCOLR Pharma partners with companies under contractual arrangements that include licensing fees, royalties, manufacturing contracts, or other mutually agreed upon financial arrangements. SCOLR Pharma's CDT® has the many distinct advantages, including highly programmable (capable of a wide range of release profiles), easy to manufacture (employs conventional manufacturing equipment), cost effective (utilizes standard tableting excipients), higher payload (when compared to other technologies), and strong patent protection (full patent life and easy enforcement). For more information, visit SCOLR Pharma at www.scolr.com.

FORMULATION TECHNOLOGY



For drug developers concerned about formulating poorly soluble compounds, SOLIQS Meltrex is the drug delivery solution. SOLIQS has adapted melt extrusion processes to the manufacture of pharmaceutical formulations, and offers its collaborating partners formulation know-how, competence in polymer and analytical research, and dedicated resources from early feasibility studies through production. Meltrex technology applies heat and pressure to a mixture of active ingredient and thermoplastic polymer. No water or other solvents are necessary. The melt is then extruded and shaped as tablets, granules, pellets, sheets, sticks, or powder. The result is improved bioavailability, specifically designed release profiles, competitive costs, and opportunities for patent protection and life cycle management, adding value to both new molecular entities and established products. SOLIQS and Meltrex are a safe solution for insoluble drug substances. For more information, contact SOLIQS at (877) 765-4771 or visit www.soliqs.com.

TRANSDERMAL DELIVERY



Established in 2000, TransPharma Medical Ltd. is a specialty pharmaceutical company focused on the development and commercialization of drug products utilizing a proprietary active transdermal drug delivery technology ViaDerm. TransPharma aims to develop multiple drug products through strategic partnerships with leading pharmaceutical companies and through

independent product development. TransPharma's ViaDerm drug delivery system incorporates a hand-held electronic control unit, which creates microscopic passageways through the outer layer of the skin allowing for transdermal delivery of a wide variety of drugs from a patch. The system provides a cost-effective, easy-to-use, self-administered solution that enables the safe, reproducible, and accurate delivery of a broad range of product candidates, including hydrophilic small molecules peptides and proteins. For more information, visit TransPharma Medical at www.transpharma-medical.com.

BLOW/FILL/SEAL MACHINE



The Asep-Tech® Model 628 Blow/Fill/Seal machine from Weiler Engineering, Inc. features a two-piece stepped-base design for easy maintenance and convenient product discharge. All existing Model 624 tooling (molds, fill

systems, parison heads) can be used on the Model 628 machine, making it an attractive upgrade for current users. The versatile Model 628 has the flexibility to produce sterile, liquid-filled, tamper-evident containers ranging in size from 0.5 mL up to 250 mL, in full-scale production quantities. Several other machine models are offered to fulfill higher output and/or larger container size requirements. The Model 628 comes complete with an integral product buffer tank designed to meet tight fill tolerances and all digital controls interfaced to a Data Acquisition System that features Wonderware® software. For more information, contact Weiler Engineering at (847) 697-4900 or visit www.weilerengineering.com.

TECHNOLOGY Showcase

DRUG DEVELOPMENT



Xcelience is the premier source for unsurpassed quality in drug development services. The company brings together the industry's most experienced and talented scientists, consistently and efficiently moving compounds through the research and development continuum to regulatory approval. Since 1997, the Tampa-based laboratory has been developing formulations for clients throughout the pharmaceutical industry. Xcelience's unique corporate structure creates project teams that work intensively with each client, bringing an extension of their own organization into the Xcelience lab. The lab uses only state-of-the-art equipment, highlighted by the patented Xcelodose[®], which fills API directly to capsules (Xcelodose is a registered trademark of Capsugel BVBA). This and other technologies give Xcelience unparalleled speed to market without compromising its absolute commitment to quality. For more information, contact Xcelience at (608) 643-4444 or visit www.xcelience.com.

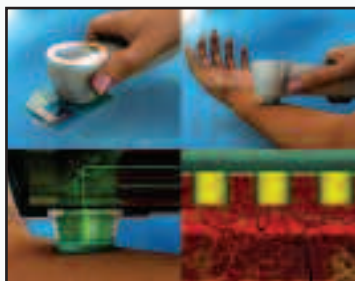
INNOVATIVE PLATFORMS



Adhesives Research has over 20 years of experience manufacturing pressure-sensitive adhesive systems for the pharmaceutical industry. Adhesives Research's custom development capabilities include polymer synthesis, adhesive mixing, compounding, coating, and release liner design, supported by analytical capabilities. The company integrates these capabilities to formulate and manufacture unique products to meet customers' specifications. The company's Pharmaceutical division

provides skin-friendly adhesives and laminate for active and passive transdermal delivery systems and pulmonary delivery applications. ARx, LLC (a wholly owned subsidiary of Adhesives Research) addresses the growing global need for innovative delivery of active drug-containing systems. ARx develops and manufactures innovative pharmaceutical products, including adhesive laminates and dissolvable films, for customized drug delivery platform technologies. For more information, contact Adhesives Research at (800) 445-6240 or visit www.adhesivesresearch.com.

INTRAEPIDERMAL DELIVERY



P.L.E.A.S.E.[®] (Painless Laser Epidermal System) is a novel transdermal delivery method for high molecular weight drugs. A hand-held laser device creates controlled aqueous micropores in the epidermis. Due to the special features of the

device, the micropores do not reach the dermis, where nerves and blood vessels reside. An intelligent graphical user interface guarantees simple and safe use by medical personnel or patients, who can use the device without supervision. A special laser source ablates outer skin tissue painlessly in a highly controlled and accurate fashion. Features and benefits include very short pulses that practically eliminate thermal damage; fast and accurate ablation of skin tissue; and scanner optics allowing for flexible formation of pore arrays. For more information, contact Pantec-Biosolutions at +423 377 13 90 or visit www.pantec-biosolutions.com.

DRUG PALATABILITY



Senopsys LLC is a specialty services firm dedicated to the development of palatable pharmaceuticals. A drug product's aesthetics (appearance, aroma, flavor, texture, mouth

feel, and ease-of-swallowing) can have a dramatic effect on compliance, health outcomes, and product sales. Senopsys partners with pharmaceutical, biotechnology, drug delivery, and CROs to optimize the sensory characteristics of medications. The company uses proprietary sensory assessment tools to identify the critical sensory attributes of drug substances, quantify taste-masking challenges, measure the palatability of drug prototypes and competing products, and develop target sensory profiles that result in patient-acceptable drug products. Senopsys also works with developers to assess the suitability of novel dosage forms and delivery technologies for specific drug substances and develop new formulation systems for investigational and approved drugs. For more information, contact Senopsys at info@senopsys.com or visit www.senopsys.com.

DRUG DELIVERY

Executive

ISIS BIOPOLYMER



Emma Durand
President & CTO

Isis Biopolymer, Inc.

"We've focused on making order of magnitude improvements in five major areas: microprocessors, thin film batteries, biopolymers, and proprietary adhesives, as well as building the patch around a software-based patient care management system that allows the healthcare provider to control activation, monitor use, and adjust dosage and delivery. Isis Biopolymer is fundamentally a materials science company that happens to be focusing in healthcare."

ISIS BIOPOLYMER, INC.: IONTOPHERETIC PATCHES IN PATIENT-FRIENDLY PACKAGES

Isis Biopolymer, Inc. was founded in 2007 with a mission to enable medical professionals and biopharmaceuticals to greatly expand the number of drugs that can be delivered non-invasively and cost effectively using transdermal drug delivery technology. The company's initial product is the Isis Patch, the first programmable, multi-day, ultra-thin, hypoallergenic, and active transdermal drug delivery system. Through advances in microprocessors, thin-film batteries, biopolymers, and proprietary adhesives, the Isis Patch is capable of delivering up to 80% of the top 200 brand name and generic drugs, while introducing a proprietary software package to allow physicians to control activation, monitor use, and adjust drug delivery to each patient. Medical professionals are frustrated with today's patches due to limitations ranging from unreliable patch adherence and local skin site problems to non-compliance and abuse issues. Isis is offering a breakthrough in the form of a much smaller, softer, more flexible, and consumer-acceptable design. Hypoallergenic, skin-friendly polymers eliminate irritation and allow the patch to be worn for longer periods with superior adherence to the skin. Isis is currently initiating clinical trials and is well along in animal trials, working with pharmaceutical companies to select specific drugs to be formulated for the Isis Patch. Additionally, the company is developing its own drug therapies, beginning with solutions for diabetes, ADHD, and others. Drug Delivery Technology recently interviewed Emma Durand, President and CTO of Isis, to discuss how the Isis Patch aims to deliver the clinical benefits of iontophoresis with the convenience and cost effectiveness of a transdermal drug patch.

Q: What do you see as the main industry and environmental factors driving the growth of transdermal drug delivery? Why is there a need for new and better approaches?

A: Two irrefutable trends are at work in our market. One is the constant pressure for cost efficiency, and the other is the corresponding movement toward self- and

home-care, especially for chronic ailments. What we already know about these patients is that they have difficulty traveling to healthcare providers as well as receiving injections and maintaining compliance. Transdermal patches have been proven as preferable over injections, which is why we already have roughly a \$2-billion market. Yet, despite over 35 products in the market today, we do not have transdermal patches that are both patient friendly and cost effective.

DRUG DELIVERY *Executive*

Q: What do you believe are the major shortcomings of conventional patches?

A: It's really been a one-size-fits-all approach, with no effective way to modulate how much or when a drug is released. Also, the size and type of drug molecule that will cross the skin barrier are limited. Adverse skin reactions to the adhesives have hurt the usability of many patches. These limitations can be addressed by iontophoresis, but the trouble has been that existing iontophoretic devices are way too bulky, uncomfortable, and difficult to use for most patients, even with training.

Q: What are the key features and benefits of the Isis Patch?

A: To begin with, the design is different. It's quite thin, 0.002 of an inch thick and made of soft and pliable polyester substrate, as opposed to the thick, plastic-covered patches we've had. It's small, soft, and very pliable. The polymers are skin friendly and adhere better without causing irritation. In addition, our hydrogels are unique and proprietary to Isis. They allow us to use more diverse drugs than are currently available. The

software interface and wireless controller are where our approach really stands out, and there are many features designed to give physicians control. A patch can hold up to three different drugs for up to 7 days of dosing. Each can be delivered at a predetermined rate, over a time period that may be programmed into the patch and subsequently retrieved to the patient's record. There are also many ease-of-use features, such as pulse dose delivery and nocturnal shut-off, which make delivery of desired dosage more reliable. Our team's background in PTF flexible circuits has led to several innovations over traditional rigid and flexible copper circuits, like our environmentally friendly manufacturing process. It can reduce the cost of conventional iontophoresis by as much as 50%.

Q: So will this lead to improved compliance?

A: Yes, because it's a painless alternative to injection that is convenient, easy to wear, and multi-day. Physicians tell us they like the ability to remotely control activation of the patch and monitor use as well as adjust drug delivery. This software-driven system helps them avoid under- and overdosing as well as misuse.

Q: How is the Isis Patch programmed?

A: Following consultation with the patient, the doctor e-mails the prescription into the patient's pharmacy (or the patch can be pre-programmed with profiled dosages). Each patch has a unique identification number for individualized tracking and follow-up. The pharmacist activates the patch and transfers the dosing information using the Isis hand-held control. The patient then applies the patch and has the option of returning it to the physician for compliance tracking.

Q: What is your go-to-market strategy?

A: We are currently working with one of the largest pharmacy chains in North America on the doctor/pharmacy interface. Our plans are to license the technology to Pharma. Engagement has already begun with three major players in this space. Additionally, Isis is developing three drug therapies for diabetes, ADHD, and movement disorders. Our strategy has been to focus on sizeable market opportunities in which we can show clear advantage to both patient and physician in a way that is just not

DRUG DELIVERY *Executive*

unattainable by conventional delivery technology. For diabetes, an Isis Patch is in feasibility studies with a goal to provide optimum 24/7 delivery of an insulin stimulator and smooth, broad dosing peaks at meal times. This delivery profile will circumvent the extreme side-effect and needle-stick pain concerns associated with current diabetes treatment. An Isis Biopolymer Patch is currently being designed for ADHD patients, with a patient-specific 7-day wear period. For patients with Tourettes Syndrome and other movement disorders, we can address the need for large and numerous dosages with a reliable, effective, and patient-friendly patch within a population that is difficult to treat.

Q: How do you view the competitive landscape in active transdermal drug delivery?

A: Clearly, we are in need of the next generation of active TDD products. Prior processes have just not proven to be cost effective and patient friendly. Electroporation, for example, is not necessarily a portable process and may require a separate power supply and a medical technician. The same

holds for heat-based TDD. Traditional iontophoresis typically has involved high cost and in many instances, requires a power supply. Microporation requires higher cost and fundamentally more complex manufacturing, and although painless, still has the stigma of needles.

Q: What are the potential therapeutic uses for the Isis Patch beyond those you mentioned?

A: Beyond chronic diseases, we will address hormone replacement, pain management, oncology, geriatrics, and pediatric and veterinary.

Q: Please tell our readers about the Isis team, and what are the next steps?

A: The Isis team has worked together in various entrepreneurial endeavors for over 20 years. We're a group with deep expertise in medical devices, materials, and systems design. We've collectively developed and licensed proprietary technology to 11 Fortune 100 companies. We are the same group of researchers that successfully developed the first mass-produced flexible

pulse oximeter in 1992. Also, we have assembled an outstanding medical advisory board with experts in advance research, hospital administration, clinical medical trials, and new drug development. Interestingly enough, our team size is based upon a study completed by the DOD a number of years back. They studied team size against quality of innovation and discovered that small teams yielded the most groundbreaking developments and subsequent value over time. Regarding our next steps, following first-customer engagement, we are submitting to the FDA, which is a much shorter process for drugs already approved for transdermal delivery. We're anticipating approval for our first product in 2011. ♦

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Biopharmaceutical Manufacturing

BioPharma Contract Manufacturing: Growth Opportunities & Strategies

By: Barath Shankar Subramanian, Industry Analyst,
Pharmaceuticals and Biotechnology, Frost & Sullivan

Contract Manufacturing is the largest segment within the pharmaceutical outsourcing market, comprising contract research organizations (CROs) and contract manufacturing organizations (CMOs). It accounted for 68% of total global pharmaceutical outsourcing revenues in 2007 (Figure 1). CMOs provide independent manufacturing services for the pharmaceutical and biotechnology markets. Services offered by CMOs have evolved from providing basic manufacturing services to a range of services that presently suit the demand of both the market and the outsourcers. The US is the world's largest market for drugs and accounts for almost half of R&D spending in the pharmaceutical and biotechnology industry. Hence, CMOs play a critical role in this market and have invested in new facilities and technologies to cater to a wide range of outsourcers.

Biopharmaceutical Manufacturing—Market Metrics

The two major types of biopharmaceuticals included within the scope of this article are those derived from mammalian and microbial cells, which are the two main market segments. Microbial-derived biopharmaceuticals are first-generation products and are typically less complex than mammalian cell-derived products.

Recently completed research by Frost & Sullivan revealed that the global biopharmaceutical contract manufacturing market is expected to grow from \$2.45 billion in 2007 to \$6.48 billion by 2014 at a compound annual growth rate of 14.9% (Figure 2).¹

Mammalian cell contract manufacturing is expected to drive growth by significantly outpacing microbial contract manufacturing. This manufacturing is expected to grow at a slower pace than the overall market due to maturing products and a stronger mammalian cell-derived drug pipeline. The manufacturing capacity for microbial fermentation is much more fragmented amongst CMOs, unlike mammalian cell culture, which is dominated by captive capacity. It is estimated that more than two-thirds of biopharmaceuticals in development are mammalian cell derived, while only one-third is microbial. This suggests why there is likely to be significant capacity addition in mammalian cell culture, while the microbial capacity addition is not expected to be major.

New Growth Areas for CMOs

There has been considerable talk about Big Pharma entering into the biopharmaceutical market through internal development, strategic licensing, and acquisitions. The manufacturing of biopharmaceuticals, however, is a major growth opportunity for CMOs as Big Pharma has made it evident the focus will be on their core strengths—development and marketing.

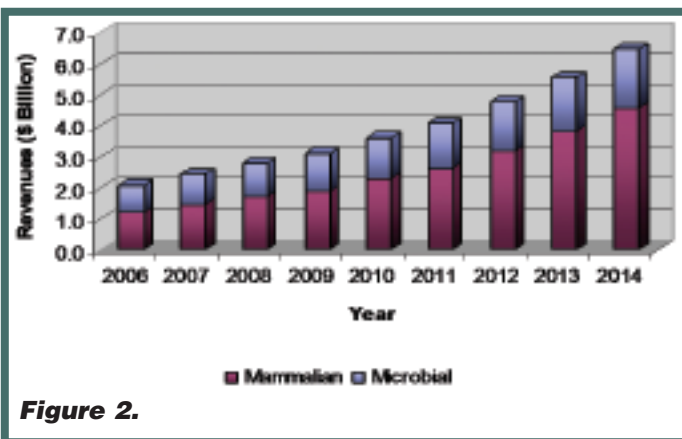
From an investment point of view, captive biopharmaceutical manufacturing is a very tricky and risky decision. The average cost of building a commercial manufacturing facility is \$400 million, and it takes 4 to 5 years

for the facility to come online. Captive manufacturing capacity has witnessed considerable growth in recent years and is expected to peak in 2009 before slowing down.

Overall capacity addition (captive + CMO), however, is actually expected to experience strong growth, suggesting significant growth from the CMO market. The strong biopharmaceutical pipeline is also expected to help drive growth, which could cause a turnaround in capacity utilization levels. Capacity utilization rates for global biopharmaceutical manufacturing declined from 73.7% in 2003 to 62.9% in 2006. However, it is expected to witness an upsurge and reach 83.8% by 2012.¹ A significant driver of this upsurge is expected to be from new molecules, especially mammalian cell-derived and more preferred service provider partnerships between CMOs and biopharmaceutical companies.

Between 2004 and 2007, the share of captive mammalian manufacturing capacity has witnessed a decline, while the top CMOs have added capacity. The percentage share of other captive manufacturers, which includes spare capacity sellers, has risen between 2004 and 2007. This could be attributed to the market consolidation, resulting in excess capacity with biopharmaceutical companies.

In terms of global revenue share, North America continues to dominate with almost 80% share in 2007 (Figure 3), while the Europe and Asia-Pacific regions are increasing their share at a rapid pace. Asia-Pacific offers a significant cost advantage with outsourced research or manufacturing savings that can range from 50% to 80%. This benefit is likely to boost the volume of outsourced work to the Asia-Pacific region.

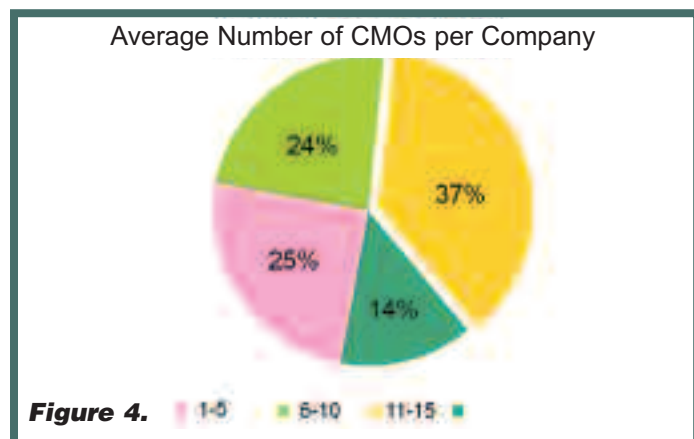
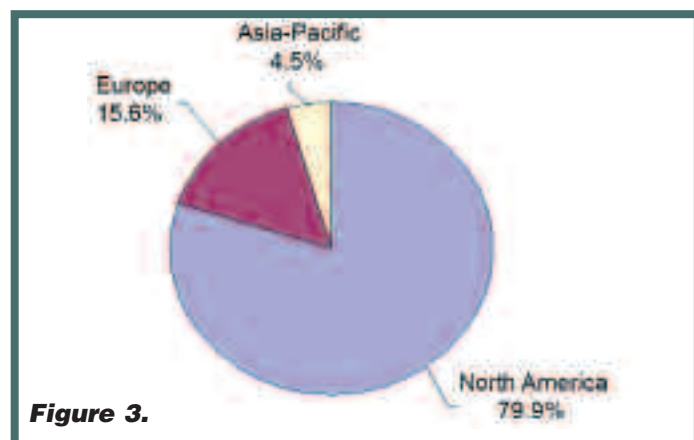


Strategies for CMOs—More Risk & More Value-Added Services

Contract manufacturing represents only 3.8% of the global biopharmaceuticals market revenues. For CMOs, the “mantra” for continued success and higher-than-average growth in a market that is significantly under-penetrated is adopting a more strategic approach to partnerships. Companies should look to provide more value-added services like development, analytical and regulatory support, packaging, logistics, and consulting services. This will help them secure longer and more closely engaged partnerships, which will benefit them in the long-term.

The contract research and manufacturing services (CRAMS) market comprises CROs and CMOs. Both groups benefit from companies looking to increase efficiency, productivity, and increased growth through life-cycle management (LCM) of products. Despite their increasing importance in the market, these service providers could benefit by moving from a purely transactional model to a strategic relationship model, such as the preferred service provider model.

From an outsourcer point-of-view, life-cycle management and sharing development risk are two important factors that are considered in choosing the product to outsource and the CMO. While more biopharmaceuticals (especially microbial derived) are maturing in sales, companies have to calculate the opportunity cost of manufacturing them in-house versus outsourcing them.



The preferred service provider approach is becoming more popular with biopharmaceutical CMOs. Companies that have enjoyed considerable success (eg, Lonza Biologics) have successfully adopted this model and built long-term partnerships. In the past, outsourcers have been reluctant to engage in such partnerships, mainly due to a mismatch in the short- and long-term goals and priorities of biopharmaceutical companies and CMOs.

Companies typically work with multiple preferred service providers (Figure 4) at any given point for a variety of reasons, including the following:

- Different service providers have different strengths and technical niches;
- It is easier to manage a range of product platforms; and
- It outweighs any potential risk of the CMO going out of business by having multiple options.

With the potential entry of biogenerics, biopharmaceutical companies and CMOs are likely to adopt a cautious approach toward the market (Figure 5). If not cautious, there could be a potential conflict of interest in integrating the outsourcing business model with an in-house product model of biogenerics from an intellectual property standpoint. Several CMOs are gearing up to the approval of a regulatory pathway for biogenerics and looking at biogenerics as a potential add-on business to their existing contract manufacturing services. This could result in a situation in which CMOs compete with biopharmaceutical companies in certain therapeutic areas while continuing to provide manufacturing services for the same companies. It will be interesting to see how the market responds to such a situation.

Positioning themselves in the right market niche is also very important for CMOs. From a small/start-up biotech perspective, those companies are increasingly looking to retain greater control over products than ever before. CMOs provide them the opportunity to do so, but the downside of working with these companies is the risk of product failure. This risk is higher at an early stage, especially if the CMO is looking to progressively expand capacity as the product moves into the development cycle. This can be addressed to a large extent by focusing on a portfolio of products, but then the issue of building a plant first versus waiting for deals to close arises.

Another potential business model for biopharmaceutical CMOs is the lease/license and operate model in which the biopharmaceutical company no longer operates or manages the facility and hands over the operations to a CMO instead. This model makes sense for a biopharmaceutical company that is looking to reduce its operating costs without having to reduce manpower, which would be transferred to the CMO. This also enables CMOs to add additional capacity, and at the same time, not spend additional money on finding and recruiting talent.

When CMOs add manufacturing capacity through new plants or expansion of existing plants, the cash flow generated through operations is expected to offset the capital expenditure,

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Summary

As biopharmaceutical companies increasingly focus on innovation, revenues, and lowering overall cost, the importance of CMOs in achieving these objectives continues to rise. As CMOs continue to work closer with biopharmaceutical companies, the next major step for them could be to drive the integration of the different strategic sourcing components through structured management of these functions. Most service providers are located in different regions of the world, having significant differences in culture, economics, politics, and regulations. These differences have often resulted in high failure rates among service providers and sponsor companies. With the increasing globalization of businesses, however, it is critical to ensure the integration of these different service providers into a partnership/risk-sharing model and drive global business capabilities.

More than 50 biopharmaceutical products are likely to be approved between 2007 and 2010, driving up capacity utilization. Capacity utilization, which witnessed a decline between 2003 and 2006, is beginning to rise and result in higher revenues from existing capacity. Lower capacity utilization has resulted in higher competition among contract manufacturers, lower revenue growth, and margin pressures.

With biopharmaceutical funding on the rise, smaller biopharmaceutical companies are more likely to consider building up their own capacity moving forward. However, the risk of failure of products is the biggest deterrent to building up captive capacity and partnering with CMOs.

As biopharmaceutical companies continue to focus on improving efficiency and productivity at lower costs, CMOs will need to achieve the same internally through better integration of services. The emergence of companies that provide integration services is a clear indicator of the market demand and potential that lies in this area. The future of the biopharmaceutical industry and its continued success and growth predominantly depends on this. It is important that companies take the lead in ensuring that the infrastructure to support integration is robust and in place. ♦

Reference

1. Frost & Sullivan Analysis, Global Biopharmaceutical Contract Manufacturing Markets. (January 2008).

Growth Strategies for CMOs in Biopharmaceutical Manufacturing

Providing Value-Added & Integrated Manufacturing Services

Preferred Service Provider Model

Positioning in the Right Market Niches

Sharing Risk in Development Stage Projects

Working Closely With Emerging & Second-Tier Biopharmaceutical Companies

Lease/License & Operate Business Model

Figure 5.



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Mr. Barath S. Subramanian is a Research Analyst with the Frost & Sullivan North American Healthcare Practice. He focuses on monitoring and analyzing emerging trends, technologies, and market behavior in the pharmaceuticals and biotechnology industries in North America. Since joining Frost & Sullivan in October 2004, Mr. Subramanian has completed several research studies and consulting projects on Pharmaceuticals and Biotechnology. Prior to this, he was a Research & Development intern at IPCA Laboratories Ltd., Mumbai, India. He brings with him considerable analytical and quantitative experience, giving him a keen perception into the functioning of technology in the healthcare industry. Mr. Subramanian has received acclaim for his research through articles and quotes published in *Specialty Pharma* and *Drug Delivery Technology* magazines.

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Targeted Tumor Therapy Using Alpha-Particle Emitters By: Thomas Ramdahl, PhD, President & CEO, Algeta ASA

Introduction

More than 50% of cancer patients receive radiotherapy, but such treatment is sub-optimal. While clearly effective at destroying tumor cells, a major drawback with any form of radiation beamed from an external source is that healthy tissues are also destroyed at the same time. This can lead to unpleasant side effects and severely limit the amount of radiotherapy that can be given. However, radiotherapy does not have to be this way.

Increasingly, molecular targeting is being used to carry carefully selected radionuclides to tumor cells specifically and accurately. Following injection, these new therapeutics seek out and bind to tumors, providing a form of highly specific radiotherapy.

A new generation of products providing targeted radioactivity that is showing particular promise both in the clinic and in research is based on the emission of alpha particles. These high-energy, ultra-short range particles are being developed to deliver lethal doses of radiation selectively to individual tumor cells while minimizing damage to neighboring normal tissues. Alpha-particle emitters are therefore expected

to have a significant role in the future treatment of cancer.

Radionuclide Therapy

The first use of radionuclides (ie, radioactive isotopes) to target and irradiate cancers from within goes back more than 50 years, but the procedure is so effective that it is still routinely used today. Radioiodine, which has a natural biochemical affinity for thyroid cells, is used to treat thyroid cancer. For patients, the treatment is very simple: they take the dose in the form of an oral capsule, which dissolves in the stomach, releasing the radionuclide that then concentrates in the thyroid and irradiates the tumor. However, in this case, there are disadvantages because the targeting mechanism does not adequately distinguish between cancer cells and normal thyroid cells.

Unlike radioiodine, most cytotoxic radionuclides have no intrinsic affinity for target tissues, and so many next-generation products engage tissue- or tumor-selective binding proteins to achieve targeted delivery. This group includes radionuclides chelated with bone-seeking phosphonates (to target

skeletal metastases) or linked via a chelator to a cell target-specific peptide or monoclonal antibody (ie, radioimmunotherapy to target neuroendocrine tumors or non-Hodgkins lymphoma).

For reasons of practicality, these approaches have up until now largely been exemplified using beta-emitting radionuclides, which typically have radiation ranges of several millimeters. Clearly, this is far from ideal as the inherent advances of specificity and selectivity that arise from using targeting agents that are selective for tumor cells are lost if the range of radioactive emission means that very substantial volumes of normal tissue are also damaged.

Alpha Versus Beta Particles

In contrast to beta-emitting radionuclides, certain alpha-particle emitters have ideal properties for targeted approaches. Evidence is mounting that they can provide a range of products with greater therapeutic benefit and more attractive safety

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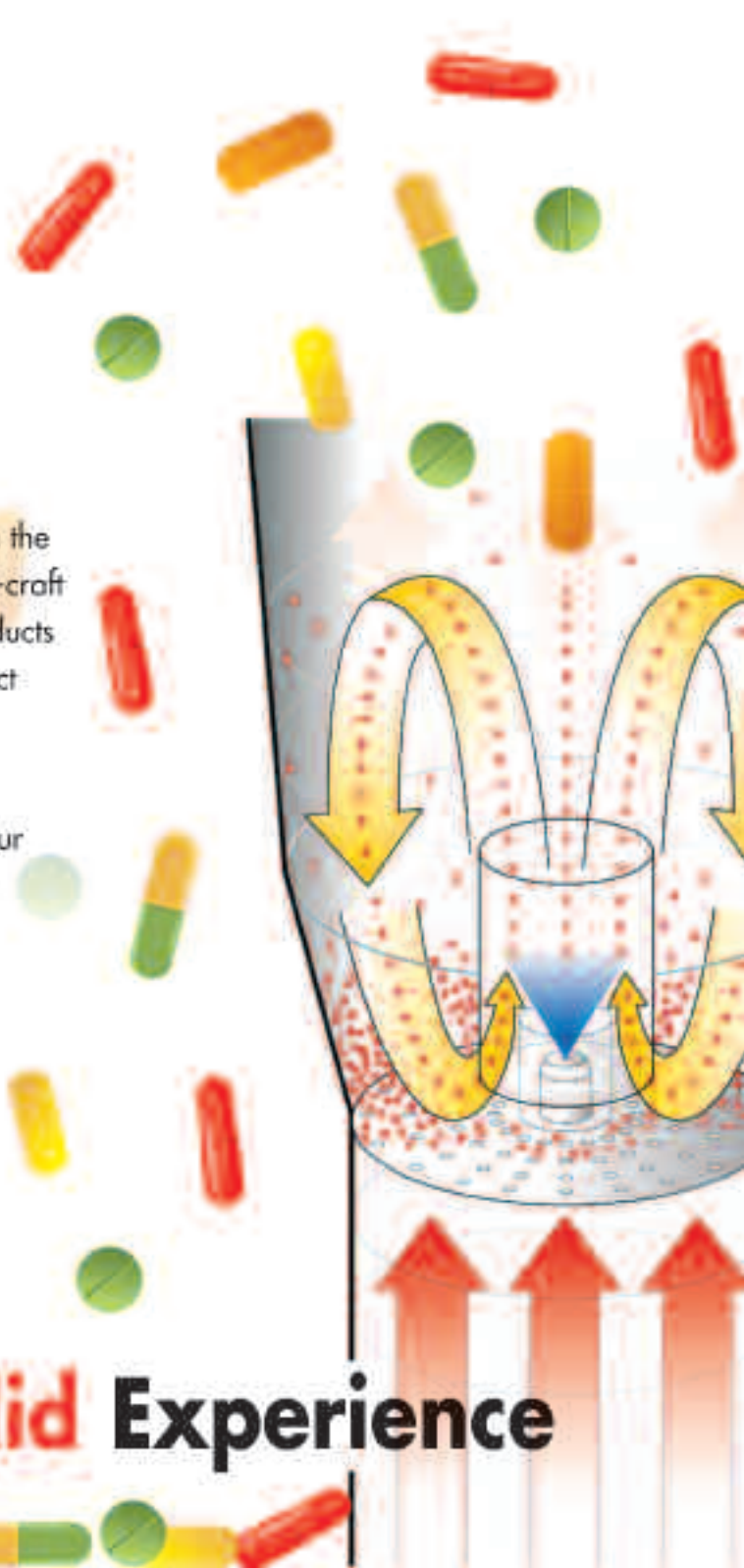


Table 1. Alpha-emitting radionuclides currently evaluated against cancer

Radionuclide	Half-Life	Development Stage
Thorium-227	18.7 days	Preclinical Phase
Radium-223	11.4 days	Clinical Phase III
Actinium-225	10.0 days	Clinical Phase I
Astatine-211	7.2 hours	Clinical Phase I
Bismuth-212	1.0 hour	Preclinical Phase
Bismuth-213	46 minutes	Clinical Phase I

profiles than many existing therapeutics.

Alpha-particle emitters exert very potent cytotoxic effects with ultra-short range. At the cellular level, their toxic potency is more than 100 times greater than that of beta emitters and on an atom-by-atom or molecule-by-molecule basis, they are among the most cytotoxic compounds in existence; fewer than five DNA hits required to kill a cell, and even a single DNA hit may be lethal.

Why are alpha-particle emitters so effective at killing tumor cells? While external beam radiation (x-ray or gamma rays) and beta-particle radiation are classified as having low linear energy transfer (LET), the high LET of alpha-particle radiation means that damage inflicted upon a cell is irreparable, and cytotoxicity per radiation absorbed dose unit is greater. Effectiveness is independent of the dose rate (ie, the time span over which the dose is delivered).

The effective range of alpha-particle radiation is typically only 2 to 10 cell diameters. This is ideally suited to cellular dimensions as it enables selective tumor cell targeting with minimal normal tissue exposure, yet does allow for the few tumor cells that do not express the molecular target to be mopped up as well.

Alpha-particle emitters may also offer advantages against the Achilles'

heel of cancer treatments—cancers that are inherently resistant or become resistant following treatment. Tumor cells typically become resistant by increasing their ability to repair themselves or by finding ways to get rid of the drug. Alternatively, they may survive by slowing down their growth in areas of the tumor where there is little oxygen. None of these maneuvers will prevent the cell-killing effects of alpha particles.

Alpharadin™

The most advanced alpha-particle emitter currently in clinical development is Algeta's Alpharadin, which is based on radium-223 and is being developed to treat advanced prostate cancer that has spread (metastasized) to the bones. Radium-223 is a calcium mimic and has an intrinsic affinity for areas of new bone whose growth is stimulated by adjacent cancer cells. This specific targeting of radium-223 to bone also suggests that it will have clinical benefit in other cancers that metastasize to the skeleton, such as breast and lung cancer, in addition to prostate cancer. Radium-223 has a half-life of 11.4 days and satisfies most, if not all, of the criteria for use as a clinical candidate (see Table 2). Important to note for practical clinical use, Alpharadin is designed to be administered by simple intravenous injection on an out-patient

basis and requires minimal shielding.

Alpharadin entered first clinical trials in Scandinavia in late 2001 and has progressed rapidly to Phase III testing. The selective nature of radium-223 and thereby its safety/tolerability in clinical use has been demonstrated across a broad dose range, where it showed no prohibitive side effects. In biodistribution studies, Alpharadin is taken up rapidly in the bone and not by other organs, and any not taken up by the bone is rapidly excreted from the body.

The clinical benefit of radium-223 was demonstrated in 2007 in Phase II efficacy trials in men with hormone-refractory prostate cancer (HRPC) that had metastasized to the skeleton. In these trials, Alpharadin treatment was found to increase the survival of men with HRPC by 40%, with more than twice as many treated patients (10 of 33) surviving 2 years after treatment began compared to those who received placebo (4 of 31).¹ Alpharadin was exceptionally well tolerated in this trial and had few clinically significant side effects.

Alpharadin treatment was also found to reduce blood levels of several biomarkers of tumor growth and bone metabolism, such as prostate-specific antigen (PSA) and alkaline phosphatase (ALP). This underpins the clinical evidence of a highly positive therapeutic effect.

Next Steps

In June 2008, Algeta began Phase III trials with Alpharadin. The ALSYMPCA trial (the acronym is derived from ALpharadin in SYMptomatic Prostate Cancer) will compare the use of Alpharadin plus best standard of care and placebo plus best standard of care. Approximately 750 patients are expected to be enrolled at more than 125 medical

centers in Europe, Asia, South America, and Canada.

The primary efficacy endpoint of the trial is overall survival, and secondary endpoints include time-to-occurrence of specified disease-related events and time-to-progression of certain key biomarkers indicative of disease status. In addition, both the acute and long-term safety of Alpharadin treatment as well as its impact on quality of life will be monitored and assessed.

An Investigational New Drug (IND) application was cleared by the US FDA in February 2008, and Algeta is initiating a Phase I pharmacokinetics, bio-distribution, and dosimetry study with Alpharadin in HRPC patients at Memorial Sloan-Kettering Cancer Center in New York. In parallel, Algeta is developing a clinical development program for Alpharadin that will support its application for approval in the US in the future.

Clinical Experience With Other Alpha Emitters in Oncology

Although it is the most advanced, Alpharadin is not the only alpha emitter with therapeutic potential (Table 1). The importance of radionuclide characteristics becomes clear when you consider what else is being investigated.

In the US, for example, researchers at Duke University have taken astatine-211-labeled chimeric 81C6 mAb into Phase I clinical trials for brain cancer. These studies provide proof-of-concept for regional targeted radiotherapy with astatine-211-labeled molecules in oncology. Specifically, the regional administration of astatine-211-ch81C6 is feasible, safe, and associated with a promising anti-tumor benefit in patients with malignant central nervous system tumors.

However, astatine-211 can only be produced at a few sites around the world (in a cyclotron) and even then only in single-patient doses. These problems are further compounded by the short half-life of the radionuclide (7.2 hours), limiting long-distance shipment of compounds. The development of astatine-211 for large-scale commercial use would therefore require new cyclotrons in the future.

Scientists at Memorial Sloan-Kettering Cancer Center have evaluated the clinical potential of bismuth-213 in cancer therapy. The half-life of this radionuclide is only 46 minutes, limiting its use to institutes at which labeling and administration of the compound can be carried out in quick succession. In addition, generator source material is difficult to obtain in amounts required for clinical trials, meaning that although

Table 2. Key Considerations When Selecting an Alpha Emitter for Therapeutic Applications

Half-Life of the Primary Radionuclide
Half-lives in the region of 10 days are considered optimal, both with regard to medical practice and in terms of the preparation and shipping of materials to hospital sites. Isotopes with short half-lives are limited to applications in which rapid administration of the radionuclide is possible and integration into target tissues is fast. Isotopes with too long half-lives create waste-management issues and, clinically, are more likely to show toxicity problems.
Half-Life of the Major Daughter Isotopes
Some alpha emitters decay via several daughter isotopes. The issue with daughter isotopes is whether the decay process enables translocation of radioactive daughter nuclides to non-target tissues, with associated toxicities. The ideal is to have daughter nuclides with very short half-lives, thereby minimizing non-target tissue radiation.
Biodistribution & Excretion
This is important both with regard to the radionuclide's biological target mechanism and the preparation and use of the final pharmaceutical product. Radium-223 has intrinsic-bone targeting properties, but other radionuclides may need to be targeted using appropriate conjugates (eg, with antibodies), depending on the tissue target.
Linker Technologies
The availability of linker technologies for the preparation of targeted conjugates (eg, antibodies) will be important for some applications.
Production of Radionuclide
Regardless of the source of the radionuclide, the nuclide separation scheme must be capable of supplying a high-purity product, both in terms of radionuclidic and chemical purity. Availability of a cost-effective and safe production methodology is critical, particularly for large-scale application. Production yield is particularly important if there is a limitation in the supply of a radionuclide.
Suitability for Shipment
Radionuclides that have short half-lives or that require extensive shielding as a result of high-energy gamma ray emissions are not suitable for shipment. Short-lived isotopes can only be used clinically if there is a local production unit close to the treatment center.

encouraging results have been obtained, bismuth-213 is currently considered unsuitable for commercial exploitation.

Recently, this group initiated a Phase I trial with actinium-225. This alpha emitter has a half-life of 10 days and has potential for development as a therapeutic. However, the generation of actinium-225 from surplus uranium-233 is currently very inefficient, and significant challenges remain if this radionuclide is to be made commercially viable.

Candidates in Preclinical Development

Meanwhile, preclinical studies conducted by Algeta and published in the hematology journal *Blood* have described how researchers from the Norwegian Radium Hospital (Oslo) in collaboration with those at the Fred Hutchinson Cancer Research Center (Seattle) and Algeta have linked thorium-227 to the mAb rituximab and demonstrated its potent antitumor effects.² Thorium-227, the parent isotope of radium-223, has a half-life of 18.7 days, and like radium-223, satisfies many of the criteria in Table 2, highlighting its potential for application in cancer therapy.

Rituximab binds to a specific molecule on the cancer cell surface called CD20 and is used for the treatment of certain types of non-Hodgkin's lymphoma and rheumatoid arthritis. In *in vitro* studies, thorium-227-rituximab killed CD20-positive lymphoma cells at low doses, while in preclinical models, a single injection of thorium-227-rituximab induced complete tumor regression in up to 60%

of tumors without apparent toxicity.

Therapy with thorium-227-rituximab was significantly more effective than the control radioimmunoconjugate thorium-227-trastuzumab, which does not bind CD20, and the standard beta-particle emitting radioimmunoconjugate for CD20-positive lymphoma, yttrium-90-tiuxetan-ibrutinomab.

Algeta is also in the early stages of evaluating the potential of radium-223 and thorium-227 linked to microparticles for targeting tumors that have disseminated into body cavities (such as from ovarian cancer) and encapsulated within liposomes for targeting soft tissue cancers.

Market Potential of Alpha Emitters

Development of alpha-particle emitters as therapeutics is primarily focused on cancer treatment. Effective therapeutics for common cancers remains one of the world's largest unmet medical needs, despite increasing understanding of the disease and availability of novel therapies.

The principle of customized, targeted therapies for the future treatment of cancer is potentially well served by recent developments in alpha-particle emitter technology. Given the range of targeting modalities through which alpha-particle emitters may be combined into products, the potential of this class of drug for broad therapeutic application in cancer is very high. Alpha emitter-based products therefore stand to have a significant impact on the oncology therapeutics market in the future. ♦

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2. Dahle J et al. *Blood.* 2007;110(6):2049-2056.



Thomas Ramdahl, PhD

President & CEO
Algeta ASA

Dr. Thomas Ramdahl is President and Chief Executive Officer of Algeta ASA, a cancer therapeutics company based in Oslo, Norway. He joined Algeta ASA in 2001. Previously, he was Senior Vice President, Operations, at Pronova Biocare AS (1998-2001) and before that, he held various positions at the senior executive level within oil and gas, petrochemicals, and pharmaceuticals in Norsk Hydro ASA. He earned his PhD in Environmental Chemistry in 1984. He can be reached at thomas.ramdahl@algeta.com.

CRO Training

Training & Testing: The Keys to Driving Study Site Performance in Clinical Trials

By: Bill Cooney, President & CEO, MedPoint Communications, Inc.

Introduction

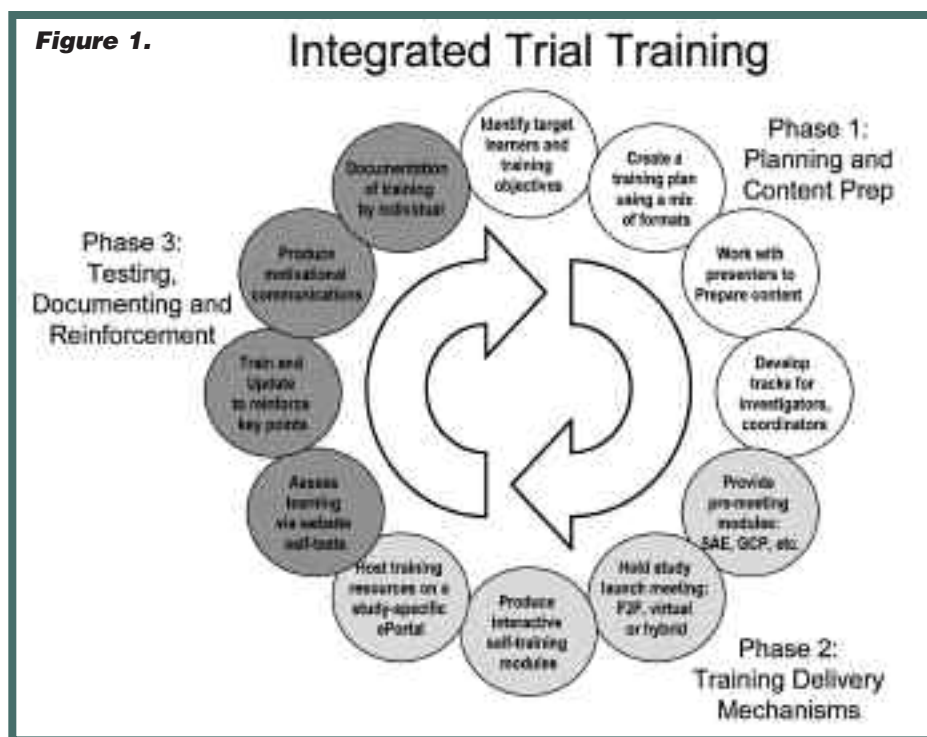
The core activity of the drug development industry is the measurement and documentation of results. Indeed, the mantra in clinical research is, "If you don't document it, it didn't happen." Despite this, very little measuring and documenting has been done in an important area of clinical research: the training of study sites to conduct individual clinical trials.

Training is an important but overlooked aspect of every clinical trial. The goal of each trial is to have several study sites conduct a complex protocol consistently and accurately. The success of the clinical trial is directly dependent on successful performance of the protocol at the site level. Yet, several trends are making it more difficult to achieve consistent site performance:

- Clinical trial protocols are becoming significantly more complex as regulatory authorities up the ante for new drug approvals;
- The technology is becoming more complex as drug developers implement more advanced systems for electronic data capture (EDC), interactive voice response systems (IVRS), and other study functions;
- Staff turnover at study sites has always been notoriously high, and this becomes a special challenge for the increasing number of long-term trials;
- Study sites are increasingly dispersed from each other, so each site is its own "training island;"
- Clinical research is expanding rapidly into new regions of the world, where there is less uniformity in English language skills, medical training, site infrastructure, and cultural settings;

- Medical-legal risk has escalated in the aftermath of alleged misconduct in clinical trials, and this has placed more regulatory pressure on principal investigators;
- The number of active trials continues to grow faster than the number of available study sites, creating more competition for sites, and busier sites that are executing multiple trials in same or similar disease states; and

Figure 1.



- Drug development costs have continued to climb, and significant cost drivers are the rates of errors and data queries to study sites.

Investigator Meetings: You're Out!

All these factors make site performance of clinical trials more challenging and more mission-critical. Drug developers must explore every avenue to improve site performance, and a major area of opportunity is in training and testing. The bad news is that prevailing practices in study-specific training have been generally poor. The Investigator Meeting has been the primary venue for training, and this approach has been sub-par on many fronts, such as:

- Training presentations have been delegated to busy study team members who often fail to apply good training practices;
- The meetings have been prolonged, one-time “data dumps” and have not been followed with good training reinforcement;
- The meetings have only included one investigator and one coordinator, and so have failed to reach the four to five professionals on average who need training at each study site; and
- There has been almost no learning assessment (testing) to complete the training cycle and produce adequate documentation of training.

The good news is that proven, effective training solutions are readily available and easy to deliver using new tools, such as websites and web conferencing. The biggest hurdle is for drug developers to recognize the need to change how they train and how study teams launch clinical trials. The old, familiar Investigator Meeting format is out. In its place is a study-specific training and testing program.

Components of a Training & Testing Program

An effective training and testing program is built upon best practices that have been established and proven by the training profession. The components of this program will reinforce each other to deliver an optimal effect on study site performance. Depending on the scope and budget of each clinical trial, however, individual training components can be dropped. The framework of a study site training and testing program are discussed further.

1. PLANNING & CONTENT PREPARATION

Study teams can benefit from the involvement of training professionals who have a strong command of adult learning principles. Training professionals can help create a solid foundation for future training by taking study team presenters through basic processes, such as identifying target learner needs and setting clear training objectives for each presentation. They can help create a long-term training program plan using a mix of formats and developing separate training tracks for investigators, coordinators, raters, and other role players. Finally, training professionals can work with presenters to re-organize their training content and improve visual design (usually in slides).

Currently, most study teams devote little time to prepare for their Investigator Meetings and subsequent activities. Investigator Meetings tend to be planned on a tight time line during a peak period when study teams are “too busy” to devote attention to good training practices. As a result, Investigator Meetings have a notorious reputation for being long and uninspiring and most ineffective from a training perspective. To break this cycle, the study team must cooperate with training professionals who can take the lead in planning and content preparation.

2. TRAINING DELIVERY MECHANISMS

Drug developers need to consider various options in how to effectively deliver study-specific training to research sites. Research has shown that effective training programs use a mix of in-person sessions,

self-learning modules, and live remote classrooms. This is known as “blended learning.” For drug developers, the options are limitless, and best choices depend on the needs of each clinical trial. However, a generic program of blended learning for study launch can be outlined.

- Develop self-learning modules for standard training topics, such as GCP and SAE. Make these available for study site members to complete as prelaunch meeting assignments. Give participants a 1-year credit for completing these modules. Consider providing a “straight-to-test” option, in consideration of investigators who have sat through numerous good clinical practice (GCP) or serious adverse events (SAE) presentations.
- Hold a “hybrid” study launch meeting where coordinators travel on-site to a hotel meeting venue and investigators participate via live video web conference. To be interactive and enjoyable, the hybrid meeting will require extensive planning and support from a capable web conference producer. This approach produces significant time savings for investigators while still allowing them to have substantial input. Other professionals at remote study sites can also participate, extending the reach of the live meeting to more target participants. This hybrid plan calls for bringing coordinators on-site for more intensive hands-on training, including use of EDC and other study systems. If the hybrid format is well planned, it can produce “best of both worlds” results in cost-savings, convenience, extended reach, and effective training.
- Capture a quality digital recording of all training presentations at the study launch meeting, and post-produce these into effective self-training modules. The modules can be improved in post-production by editing and cleaning tracks, simple builds and animations, and with the addition of scrolling text of presenter commentary. Training modules are a

critical component of the campaign to achieve high rates of documented training completion. The modules can be used to extend training to site members who missed the launch meeting or professional staff who join study sites during trial execution. The training modules are an excellent reference and refresher resource for study site members, especially for clinical trials of long duration. Lastly, training modules can improve comprehension for English-as-a-second-language learners, who can read as they listen, and slow down the pace using pause and replay functions.

- Place all training resources on the Training Management Center (TMC) of a study-dedicated ePortal website. A secure, password-protected website is the most timely and efficient way to distribute training modules and other training materials to the study sites. An ePortal can support individual log-on and track the activities of all users. In the TMC, the ePortal can track completion of training modules by an individual. Credit for completing modules can be displayed on a “scoreboard” for each individual, and data can also appear in real-time summary reports for viewing by clinical research associates (CRAs) and study team members.

3. TESTING, DOCUMENTING & REINFORCEMENT

In recent years, many drug developers have implemented hybrid meetings, training modules, and study-specific ePortals, but few have followed through with programs that test, track, and reinforce training. This is the next area of opportunity to improve site performance.

Once a study team has invested in producing training modules, a logical next step is to attach a multiple-choice test to each module. Self-tests should be prepared by an experienced training professional to produce valid measurements of learning. Allowing learners to quickly revisit material and re-test is a sensible strategy to achieve high rates of training completion.

To date, most drug developers have not required “testing out” on study-specific

training. Learning assessment (testing) produces a host of benefits, including more motivation for all participants, identifying sites that require more reinforcement, and providing feedback to improve overall training content. But the bottom line is that testing will improve training, improve performance, and ultimately improve the trial. Reinforcement is perhaps the most overlooked aspect of training in clinical trials. Sustained improvements in site performance cannot be accomplished by a one-time intervention, such as a study launch meeting. Various activities are useful to reinforce training and performance. This includes a series of periodic update conferences that provide study news, address site issues, and reinforce key training points. A communication program can be driven by a study ePortal, eNewsletters, and email polling questions.

Simulation modules are especially effective training reinforcement tools. They allow the user to simulate study-specific tasks, such as completing case report forms or applying exclusion/inclusion criteria to simulated patients. The modules can be developed so that users get feedback and reinforcement as they proceed through the simulation. User responses can be tracked and users can gain credit for successful completion. Simulation modules are powerful tools to drive performance because participants must apply knowledge to complete specific study tasks. Successful completion of simulation modules is perhaps the single-most valid measurement of effective training.

Performance, it is said, is driven by more than training alone—people must be motivated. Study site professionals are compelled by various motivations, including altruism, affiliation, and pride. Human interest stories, modest reminder items, “scoreboards” showing statistics by site, and public relations messages can all help drive site performance. A motivational program should include mechanisms that solicit feedback from sites, such as email polling, open forums, and ePortal-posted questions.

The final phase of the training program is to document high levels of training/testing completion. A Training Management Center (TMC) on the ePortal facilitates documentation. As individuals complete each assignment, the

ePortal can track completion and post credits to each person’s training scoreboard. To motivate users, the TMC can also process and forward electronic course completion certificates. The TMC can automatically generate personalized emails reminding users to complete overdue assignments. CRAs and study team members can view summarized scoreboards of training/testing completion and intervene as needed.

Documentation should be captured in a central database that is compliant with 21 CFR Part 11. A comprehensive system of driving and documenting study-specific site training addresses many concerns of regulatory agencies, especially regarding protecting the safety of patients being treated with novel investigational products.

Summary

In summary, study-specific training and testing has been acutely under-served in clinical research. There is an array of proven training formats that drug developers can tap into to address this “training gap.” A comprehensive training/testing program represents a major opportunity for drug developers to significantly improve study site performance, leading directly to faster, higher quality, lower cost clinical trials. ♦



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EXTERNAL DELIVERY

Blatant Political Partisan Tones?

By: Dan Marino, MSc

I recently received the following letter from a reader:

Mr. Marino,

While I find Drug Delivery Technology an informative and technically balanced magazine, which recently has improved in the technical quality of its articles, I am offended by the blatant political partisan tone of the Executive Delivery, Rome is Burning!, by Mr. Bermingham. I am distressed that politics should be addressed at all in a scientific publication, but such a biased article is completely unprofessional and inappropriate.

I responded with the following:

Dear Ms. Pelosi (the name was changed to protect the innocent),

Thank you for your letter and taking the time to write me, it is always welcomed and appreciated. Based on the ongoing active participation and guidance of our esteemed editorial advisory board, who reviews, submits, and recruits articles, unlike other magazines that just list names on their boards, I would hope that the quality of the content of our business-to-business magazine would steadily improve. We strive to publish an ideal mix of review, technology application, and research articles. We are always looking for feedback and constructive criticism. If you wish to participate with us in the future or have any specific suggestions, I would welcome those. Ms. Pelosi, I went back and read the column Rome is Burning again to look for partisan (let alone blatant political partisan) verbiage and was unable to locate any such language. We have no political affiliation nor do we promote any political party in our publication. Can you please let me know

what specifically you are referring to in the column; it would be helpful to me in preventing such language from Mr. Bermingham in the future. Thank you. Looking forward to hearing from you.

I believe Ms. Pelosi is confused between partisan politics and using facts to make a comparison. Mr. Bermingham was simply using a current event in the House of Representatives to make a point in the business world, particularly the actions of CEOs. He stated no ideology, disparaged no political party, etc. He did use the name Nancy Pelosi, but that is because she is the Speaker of the House. If Mr. Bermingham had used some obscure Representative's name, some impact would have been lost. We apologize that Nancy Pelosi is a Democrat and it was her party that left a session of Congress for the factual reasons Mr. Bermingham stated, but that is only a coincidence. Mr. Bermingham would have made his Congressional comparison even if it were a Republican who was the Speaker of the House.

I personally take offense that I was accused of being blatant, which means we had some sort of an agenda, which we did not. If Ms. Pelosi is offended by blatant partisan politics, then she must be offended every time she turns on the radio, computer, or television because all I hear any politician doing these days is pointing the finger at the other party and making gross exaggerations, stating unobtainable promises, and supporting legislation to bolster their party's own ideology, not the good of the people, which is indeed blatant partisan politics. I don't have to guess what political party Ms. Pelosi favors; it is very apparent from her letter to me. And why do I know this? Because she did not write me back to support her accusation with facts, which is typical of her party. (By the way, my last statement is a PERFECT example of blatant partisan politics). ♦

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